IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Teruo OKU et al.
Serial No. 09/869,135 Group Art Unit 1626
Filed October 29, 2002 Examiner STOCKTON, LAURA
For : IMIDAZOLE COMPOUNDS AND MEDICINAL USE THEREOF

TRANSLATOR'S DECLARATION

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of the certified copy of Japanese Patent Application No. 367362/1998 filed on December 24, 1998; and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 24th day of September, 2003.

Ritsuko Arimura

Ritsuko Arimura

(Translation)

P A T E N T O F F I C E

J A P A N E S E G O V E R N M E N T

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application : December 24, 1998

Application Number : 367362/1998

Applicant(s) : Fujisawa Pharmaceutical Co., Ltd.

January 21, 2000

Commissioner, Patent Office
Takahiko Kondo
Certificate No. Hei 11-3095537

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【Number of Claims】 6
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【Document】 Specification One copy
【Document】 Abstract One copy
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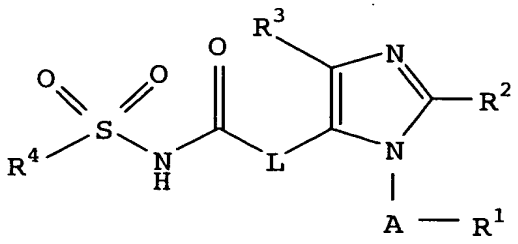
【Document】 SPECIFICATION

【Title of the Invention】 Imidazole Compound And Pharmaceutical Use Thereof

【What is Claimed is】

【Claim 1】 An imidazole compound of the formula (I):



(I)

wherein

R^1 is an aryl or heterocyclic group substituted by a substituent selected from the group consisting of (1) aryl, (2) heterocyclic group, (3) halogen, (4) halo(lower)alkyl, (5) lower alkylthio, (6) nitro, (7) lower alkenyl optionally substituted by aryl, (8) lower alkynyl optionally substituted by aryl, (9) lower alkoxy optionally substituted by cyclo(lower)alkyl or aryl, (10) aryloxy and (11) amino optionally substituted by protected carboxy or lower alkyl;

R^2 is a lower alkyl;

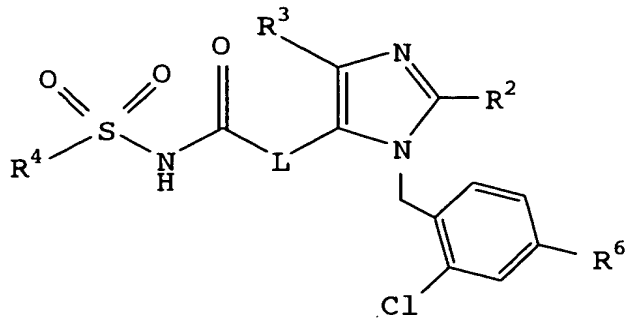
R^3 is a halogen, lower alkyl or nitro;

R^4 is (1) a lower alkenyl optionally substituted by aryl or heterocyclic group, (2) aryl optionally substituted by lower alkenyl, (3) lower alkyl, or (4) heterocyclic group optionally substituted by halogen;

A is a lower alkylene; and

L is a lower alkenylene or lower alkylene optionally substituted by aryl or heterocyclic group, or $-X-CH_2-$ wherein X is -O-, NR^5 wherein R^5 is hydrogen or lower alkyl, or -S-, or a salt thereof.

【Claim 2】 A compound of the formula (IA):



(IA)

wherein

R^2 is methyl;

R^3 is chlorine;

R^4 is (1) lower alkenyl optionally substituted by aryl, (2) aryl, (3) lower alkyl, or (4) heterocyclic group optionally substituted by halogen;

R^6 is (1) aryl, (2) heterocyclic group, (3) bromine, (4) halo(lower)alkyl, (5) lower alkylthio, (6) nitro, (7) lower alkenyl substituted by aryl, (8) lower alkynyl substituted by aryl, (9) lower alkoxy optionally substituted by cyclo(lower)alkyl or aryl, (10) aryloxy, or (11) amino optionally substituted by protected carboxy or lower alkyl; and

A is ethenylene,

or a salt thereof.

【Claim 3】 The imidazole compound of claim 2, wherein R^4 is aryl, or lower alkenyl optionally substituted by aryl, R^6 is bromine, lower alkenyl substituted by aryl, lower alkynyl substituted by aryl, or lower alkoxy optionally substituted by cyclo(lower)alkyl, or a salt thereof.

【Claim 4】 The imidazole compound of claim 1, wherein R^1 is heterocyclic group substituted by a substituent selected from the group consisting of (1) aryl, (2) heterocyclic group, (3) halogen, (4) halo(lower)alkyl, (5) lower alkylthio, (6) nitro, (7) lower alkenyl optionally substituted by aryl, (8) lower alkynyl optionally substituted by aryl, (9) lower alkoxy optionally substituted by cyclo(lower)alkyl or aryl, (10) aryloxy and (11) amino optionally substituted by protected carboxy or lower alkyl, or a salt thereof.

【Claim 5】 The imidazole compound of claim 1, which is a member selected from the group consisting of (E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-

5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-N-(1-pentanesulfonyl)-2-propenamide,
(E)-N-benzenesulfonyl-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenamide,
(E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-N-(5-chloro-2-thienyl)sulfonyl)-2-propenamide,
(E)-N-(5-bromo-2-thienyl)sulfonyl-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-2-propenamide,
(E)-3-((4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-

propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-(1-pentanesulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,

(2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide and
(2E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
or a salt thereof.

【Claim 6】 A pharmaceutical composition containing the imidazole compound of claim 1 or a pharmaceutically acceptable salt thereof.

【Detailed Description of the Invention】

【Technical Field to which the Invention pertains】

The present invention relates to novel imidazole compounds. More particularly, the present invention relates to novel imidazole compounds and salts thereof having hypoglycemic activity or PDE-V inhibitory activity. Moreover, the present invention relates to a method for producing the above-mentioned imidazole compounds and salts thereof. The present invention also relates to pharmaceutical compositions comprising the above-mentioned imidazole compound or a salt thereof as an active ingredient.

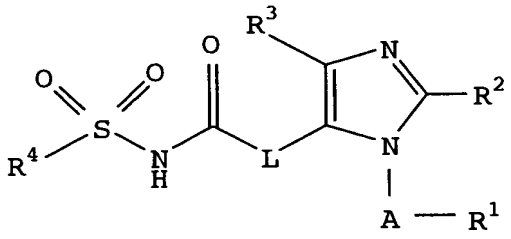
【Prior Art・Problems to be Solved by the Invention】

The present invention aims at providing novel imidazole compounds, pharmaceutically acceptable salts thereof and pharmaceutical preparations comprising the above-mentioned imidazole compound or a pharmaceutically acceptable salt thereof as an active ingredient, which can be used for the prophylaxis and treatment of impaired glucose tolerance disorder, diabetes (e.g., type II diabetes), diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic bone resorption, diabetic glomerulosclerosis, diabetic nephropathy, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy and the like), insulin resistant syndrome (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberlig-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly and the like), polycystic ovary syndrome, hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure and the like), hyperglycemia (e.g., those characterized by abnormal saccharometabolism such as feeding disorders) and hypertension; and

based on the cGMP-PDE (particularly PDE-V) inhibitory action, smooth muscle relaxing action, bronchodilating action, vasodilating action, smooth muscle cell inhibitory action, allergy inhibitory action and the like, can be used for angina pectoris, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis), tubulointerstitial disorders (e.g., kidney diseases induced by FK506, cyclosporin and the like), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma inclusive of chronic asthma and allergic asthma), autoimmune diseases, allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility (e.g., hypersensitive enteropathy), impotence (e.g., organic impotence, psychic impotence and the like), nephritis, cancer cachexia or restenosis after PTCA, pancreatitis, cachexia (e.g., progressive weight loss due to lipolysis, myolysis, anemia, edema, anorexia and the like in chronic diseases such as cancer, tuberculosis, endocrine diseases and AIDS), and the like.

【Means of Solving the Problems】

The imidazole compound [hereinafter to be also referred to as the objective compound (I)], which is the novel compound of the present invention has the formula (I):



(I)

wherein

R^1 is an aryl or heterocyclic group substituted by a substituent selected from the group consisting of (1) aryl, (2) heterocyclic group, (3) halogen, (4) halo(lower)alkyl, (5) lower alkylthio, (6) nitro, (7) lower alkenyl optionally substituted by aryl, (8) lower alkynyl optionally substituted by aryl, (9) lower alkoxy optionally substituted by cyclo(lower)alkyl or aryl, (10) aryloxy and (11) amino optionally substituted by protected carboxy or lower alkyl;

R^2 is a lower alkyl;

R^3 is a halogen, lower alkyl or nitro;

R^4 is (1) a lower alkenyl optionally substituted by aryl or heterocyclic group, (2) aryl optionally substituted by lower alkenyl, (3) lower alkyl, or (4) heterocyclic group optionally substituted by halogen;

A is a lower alkylene; and

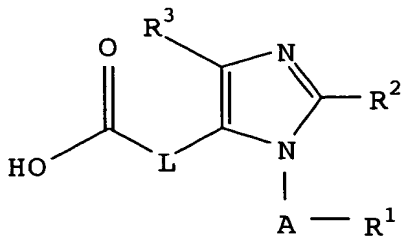
L is a lower alkenylene or lower alkylene optionally substituted by aryl or heterocyclic group, or $-X-CH_2-$ wherein X is -O-, NR^5 wherein R^5 is hydrogen or lower alkyl, or -S-.

【Embodiment of the Invention】

Preferred salts of the objective compound (I) are conventional salts that are non-toxic and acceptable for use as pharmaceuticals. Examples thereof include salts of alkali metal such as sodium and potassium, salts of alkaline earth metal such as calcium and magnesium, salts with inorganic base such as ammonium salt, salts with organic amine such as triethylamine, pyridine, picoline, ethanolamine and triethanolamine, salts with inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid, salts with organic carboxylic acid such as formic acid, acetic acid, trifluoroacetic acid, maleic acid and tartaric acid, addition salts with sulfonic acid such as methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid, salts with base such as arginine, and addition salts with acidic amino acid such as aspartic acid and glutamic acid.

The objective compound (I) and a salt thereof of the present invention can be produced by the method shown by the following reaction formulas.

Production Method 1:

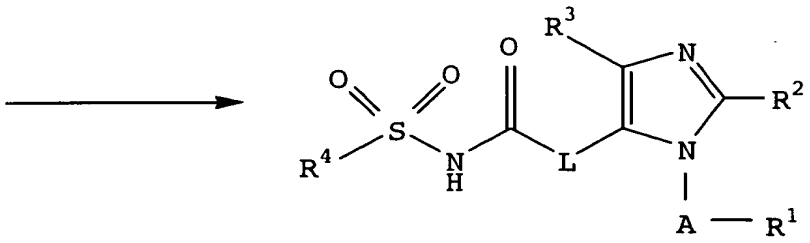


(II)

or reactive derivative at carboxyl group thereof, or their salts

+ $R^4-SO_2NH_2$ (III)

or a salt thereof



(I)

or a salt thereof

wherein each symbol in the formulas is as defined above.

Various definitions included in the entire specification are explained in detail in the following.

"Lower" means 1 to 6 carbon atoms, unless otherwise specified.

"Alkyl" and "alkyl moiety" are each preferably linear or branched alkyl. Specific examples include methyl, ethyl, 1-propyl, i-propyl, 1-butyl, i-butyl, t-butyl, sec-butyl, 1-pentyl, i-pentyl, sec-pentyl, t-pentyl, methylbutyl, 1,1-dimethylpropyl, 1-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1-ethyl-1-methylpropyl, 1-heptyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-ethylpentyl, 2-ethylpentyl, 3-ethylpentyl, 4-ethylpentyl, 1,1-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1-propylbutyl, 1-octyl, 1-methylheptyl, 2-methylheptyl, 3-methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 1-ethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 5-ethylhexyl, 5-ethylhexyl, 1,1-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 5,5-dimethylhexyl, 1-propylpentyl, 2-propylpentyl and the like.

Of these, particularly preferred is alkyl having 1 to 6 carbon atoms.

"Alkenyl" and "alkenyl moiety" are preferably exemplified by linear or branched alkenyl, such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl and the like.

Of these, preferred is alkenyl having 2 to 6 carbon atoms, and more preferably ethenyl.

"Cyclo(lower)alkyl" is cycloalkyl having 3 to 10, preferably 3 to 7, carbon atoms. Examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, with preference given to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Examples of preferable "lower alkylene" include methylene, ethylene, propylene, butylene, pentylene, hexylene and the like, with particular preference given to alkylene having up to 4 carbon atoms. Of these, particularly preferred is methylene.

Examples of preferable lower alkynyl include linear or branched alkynyl, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-methyl-3-butynyl, 1,1-dimethyl-2-butynyl, 1-hexynyl, 5-hexynyl and the like.

Of these, particularly preferred is alkynyl having 2 to 6 carbon atoms, which is more preferably ethynyl.

Examples of preferable "lower alkenylene" include linear or branched alkenylene, such as ethenylene, 1-propenylene, 2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, 4-pentenylene, 1-hexenylene, 2-hexenylene, 3-hexenylene, 4-hexenylene, 5-hexenylene, methyl ethenylene, ethyl ethenylene and the like.

Of these, particularly preferred is alkenylene having up to 4 carbon atoms, more preferably ethenylene.

"Lower alkoxy" is linear or branched alkyloxy having up to 6 carbon atoms. Preferable examples thereof include methoxy, ethoxy, 1-propyloxy, isopropyloxy, 1-butyloxy, i-butyloxy, sec-butyloxy, t-butyloxy, 1-pentoxy, i-pentoxy, sec-pentoxy, t-pentoxy, 2-methylbutoxy, 1-hexyloxy, i-hexyloxy, t-hexyloxy, sec-hexyloxy, 2-methylpentoxy, 3-methylpentoxy, 1-ethylbutyloxy, 2-ethylbutyloxy, 1,1-dimethylbutyloxy, 2,2-dimethylbutyloxy, 3,3-dimethylbutyloxy, 1-ethyl-1-methylpropyloxy, and the like.

More preferred is alkoxy having up to 5 carbon atoms, such as methoxy, ethoxy, 1-propyloxy, isopropyloxy, 1-butyloxy, i-butyloxy, sec-butyloxy, t-butyloxy, 1-pentoxy and the like.

"Halogen" is exemplified by fluorine atom, chlorine atom, bromine atom and iodine atom.

"Halo(lower)alkyl" is a linear or branched alkyl having up to 6 carbon atoms, which is substituted by fluorine atom, chlorine atom,

bromine atom or iodine atom, and is preferably exemplified by a linear or branched alkyl having up to 6 carbon atoms, which is substituted by fluorine atom, chlorine atom or bromine atom. Examples thereof include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1-fluoroethyl, 1-chloroethyl, 1-bromoethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 1,2-difluoroethyl, 1,2-dichloroethyl, 1,2-dibromoethyl, 2,2,2-trifluoroethyl, heptafluoroethyl, 1-fluoropropyl, 1-chloropropyl, 1-bromopropyl, 2-fluoropropyl, 2-chloropropyl, 2-bromopropyl, 3-fluoropropyl, 3-chloropropyl, 3-bromopropyl, 1,2-difluoropropyl, 1,2-dichloropropyl, 1,2-dibromopropyl, 2,3-difluoropropyl, 2,3-dichloropropyl, 2,3-dibromopropyl, 3,3,3-trifluoropropyl, 2,2,3,3,3-pentafluoropropyl, 2-fluorobutyl, 2-chlorobutyl, 2-bromobutyl, 4-fluorobutyl, 4-chlorobutyl, 4-bromobutyl, 4,4,4-trifluorobutyl, 2,2,3,3,4,4,4-heptafluorobutyl, perfluorobutyl, 2-fluoropentyl, 2-chloropentyl, 2-bromopentyl, 5-fluoropentyl, 5-chloropentyl, 5-bromopentyl, perfluoropentyl, 2-fluorohexyl, 2-chlorohexyl, 2-bromohexyl, 6-fluorohexyl, 6-chlorohexyl, 6-bromohexyl, perfluorohexyl and the like.

"Lower alkylthio" is a linear or branched alkylthio having up to 6 carbon atoms, which is exemplified by methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, sec-butylthio, t-butylthio, n-pentylthio, i-pentylthio, sec-pentylthio, t-pentylthio, 2-methylbutylthio, n-hexylthio, i-hexylthio, t-hexylthio, sec-hexylthio, 2-methylpentylthio, 3-methylpentylthio, 1-ethylbutylthio, 2-ethylbutylthio, 1,1-dimethylbutylthio, 2,2-dimethylbutylthio, 3,3-dimethylbutylthio, 1-ethyl-1-methylpropylthio and the like.

More preferably, alkylthio having up to 4 carbon atoms, such as methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, sec-butylthio, t-butylthio and the like, is exemplified.

In the present specification, "aryl" and "aryl moiety" are each unsubstituted aryl or aryl substituted by alkyl. Examples of preferable unsubstituted aryl include C_6 - C_{10} aryl, such as phenyl, naphthyl and pentalenyl. Of these, preferred are phenyl and naphthyl.

"Alkyl-substituted aryl" means aryl substituted by at least one alkyl. The number of alkyl substituents is preferably 1 to 4. The

aryl moiety of "alkyl-substituted aryl" is the same as for the aforementioned unsubstituted aryl, and the "alkyl moiety" is as defined above, which is preferably lower alkyl. Examples of preferable alkyl-substituted aryl include tolyl, xylyl, mesityl, ethylphenyl, propylphenyl and the like, with more preference given to p-tolyl.

"Heterocyclic group" is a saturated or unsaturated, heteromonocyclic or heteropolycyclic group having at least one hetero atom, such as oxygen atom, sulfur atom, nitrogen atom and selenium atom. Particularly, unsaturated heteromonocyclic group is preferable. More preferred are the heterocyclic groups described in the below-mentioned (1), (7) and (9), which are particularly preferably thienyl and furyl.

Heteromonocyclic group includes the following.

(1) Unsaturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having 1 to 4 nitrogen atoms, such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl and 2H-1,2,3-triazolyl), tetrazolyl (e.g., 1H-tetrazolyl and 2H-tetrazolyl) and the like.

(2) Saturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having 1 to 4 nitrogen atoms, such as pyrrolidinyl, imidazolidinyl, piperidyl, pyperazinyl and the like.

(3) Unsaturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, such as oxazolyl, isooxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl and 1,2,5-oxadiazolyl) and the like.

(4) Saturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic having 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, such as morpholinyl, sydnonyl and the like.

(5) Unsaturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl and 1,2,5-thiadiazolyl), dihydrothiazinyl and the like.

(6) Saturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolidinyl and the like.

(7) Unsaturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having 1 or 2 sulfur atoms, such as thienyl, dihydrodithinyl, dihydrodithionyl and the like.

(8) Saturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having 1 or 2 oxygen atoms, such as tetrahydrofuryl, tetrahydropyranyl and the like.

(9) Unsaturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having one oxygen atom, such as furyl and the like.

(10) Spiroheterocyclic group having 1 or 2 oxygen atoms, such as dioxaspiroundecanyl (e.g., 1,5-dioxaspiro[5,5]undecanyl) and the like.

(11) Unsaturated 3 to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group having one oxygen atom and 1 or 2 sulfur atoms, such as dihydroxathinyl.

Examples of heteropolycyclic group include the following.

(12) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group having 1 to 4 nitrogen atoms.

Specific examples thereof include benzimidazolyl, indolyl, 2,3-dihydrobenzimidazolyl, pyrazolopyrimidinyl (e.g., pyrazolo[1,5-a]pyrimidinyl), tetrahydropyrazolopyrimidinyl (e.g., 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidinyl), imidazopyrazolyl (e.g., 4H-imidazo[1,2-b]pyrazolyl), dihydroimidazopyrazolyl (e.g., 2,3-dihydroimidazo[1,2-b]pyrazolyl), imidazopyridyl (e.g., imidazo[1,5-a] (or [1,2-a] or [3,4-a])pyridyl, 1H (or 3H)-imidazo[4,5-b] (or [4,5-c])pyridyl), pyrolopyridyl (e.g., 1H-pyrolo[3,2-b]pyridyl), pyrazolopyridyl (e.g., pyrazolo[1,5-a] (or [2,3-a]pyridyl, 1H (or 2H)-pyrazolo[4,3-b]pyridyl), benzopyrazolyl (e.g., 1H (or 2H)-benzo[c]pyrazolyl), dihydrobenzimidazolyl, benzotriazolyl (e.g., benzo[d][1H-1,2,3]triazolyl), indolidinyl, isoindolyl (e.g., 1H-isoindolyl), indazolyl (e.g., 1H (or 2H or 3H)-indazolyl), indolinyl, isoindolinyl, purinyl, quinolidinyl (e.g., 4H-quinolidinyl), isoquinolyl, quinolyl, phthaladinyl, naphthalidinyl (e.g., 1,8-naphthalidinyl), quinoxalinyl, dihydroquinoxalinyl (e.g., 1,2-dihydroquinoxalinyl), tetrahydroquinoxalinyl (e.g., 1,2,3,4-tetrahydroquinoxalinyl), quinazolinyl, dihydroquinazolinyl (e.g., 1,4 (or 3,4)-dihydro-

quinazolinyl), tetrahydroquinazolinyl (e.g., 1,2,3,4-tetrahydroquinazolinyl), cinnolinyl, pteridinyl, pyrazinopyridazinyl (e.g., pyrazino[2,3-d]pyridazinyl), imidazotriazinyl (e.g., imidazo[1,2-b][1,2,4] triazinyl, imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazinyl), imidazopyrimidine (e.g., 3H-purine and imidazo[1,5-a] (or [3,4-a])pyrimidine), imidazopyridazinyl (e.g., imidazo[2,3-b] (or [3,4-b])pyridazinyl), 1H-1-(or 2)pyrimidinyl and the like.

(13) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group having 1 to 3 oxygen atoms.

Specific examples thereof include benzofuranyl (e.g., benzo[b] (or [c])furanyl), isobenzofuranyl, furopyridyl, chromenyl (e.g., 2H-chromenyl), chromanyl, isochromanyl, benzoxepinyl (e.g., 3-benzoxepinyl), cyclopentapyranyl (e.g., cyclopenta[b]pyranyl), furopyranyl (e.g., 2H-furo[3,2-b]pyranyl, and the like.

(14) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group having 1 to 3 sulfur atoms.

Specific examples thereof include benzothiophenyl (e.g., benzo[b]thiophenyl), dihydrodithianaphthalenyl (e.g., 4H-1,3-dithianaphthalenyl), dithianaphthalenyl (e.g., 1,4-dithianaphthalenyl) and the like.

(15) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group having 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms.

Specific examples thereof include dioxoloimidazolyl (e.g., 4H-1,3-dioxolo[4,5-d]imidazolyl, benzoxazinyl (e.g., 4H-3,1-benzoxazinyl), pyridooxazinyl (e.g., 5H-pyrido[2,3-d]oxazinyl), pyrazolooxazolyl (e.g., 1H-pyrazolo[4,3-d]oxazolyl), furopyridyl, and the like.

(16) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group having 1 to 3 nitrogen atoms and 1 or 2 sulfur atoms.

Specific examples thereof include thienoimidazolyl (e.g., thieno[2,3-d]imidazolyl), thienopyridyl, dithiadiazaindanyl (e.g., 2,3-dithia-1,5-diazaindanyl) and the like.

(17) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group

having 1 to 3 oxygen atoms and 1 or 2 sulfur atoms.

Specific examples thereof include thienofuranyl (e.g., thieno[2,3-b]furanyl), and the like.

(18) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group having 1 nitrogen atom, 1 oxygen atom and 1 sulfur atom.

Specific examples thereof include oxathiolopyrrolyl (e.g., 4H[1,3]-oxathiolo[5,4-b]pyrrolyl, and the like.

(19) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group having 1 or 2 selenium atoms.

Specific examples thereof include benzoselenophenyl (e.g., benzo[b] (or [c])selenophenyl), and the like.

(20) Saturated or unsaturated 7 to 12-membered (more preferably 8 to 10-membered) heteropolycyclic (more preferably heterodicyclic) group having 1 or 2 selenium atoms and 1 to 3 nitrogen atoms.

Specific examples thereof include selenopyridyl (e.g., seleno[3,2-b]pyridyl), and the like.

The preferable "aryl moiety" of "aryloxy" is the above-mentioned aryl moiety, which is more preferably phenyl.

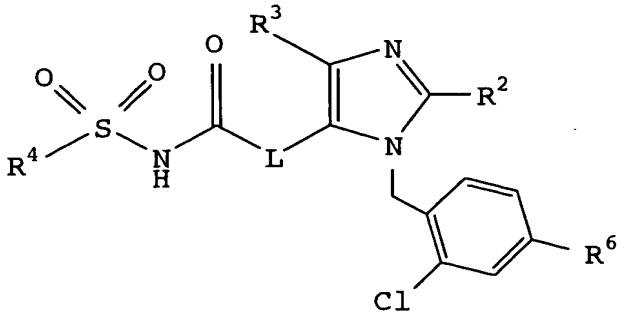
"Protected carboxy" is preferably esterified carboxy.

Examples of preferable ester moiety of the esterified carboxy include lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and hexyl ester. These groups may have at least one appropriate substituent, which is exemplified by (lower)alkanoyloxy(lower)alkyl ester such as acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1 (or 2)-acetoxyethyl ester, 1 (or 2 or 3)-acetoxypropyl ester, 1 (or 2 or 3 or 4)-acetoxybutyl ester, 1 (or 2)-propionyloxyethyl ester, 1 (or 2 or 3)-propionyloxypropyl ester, 1 (or 2)-butyryloxyethyl ester, 1 (or 2)-isobutyryloxyethyl ester, 1 (or 2)-pivaloyloxyethyl ester, 1 (or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1 (or 2)-pentanoyloxyethyl ester), and the like, lower alkanesulfonyl(lower)alkyl ester (e.g., 2-mesylethyl ester), mono- (or di- or tri)halo(lower)alkyl ester (e.g., 2-iodoethyl ester and

2,2,2-trichloroethyl ester), lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester and 1-isopropoxycarbonyloxyethyl ester), phthalidilidene-(lower)alkyl ester and (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester (e.g., (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester and (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester);
lower alkenyl ester (e.g., vinyl ester and allyl ester);
lower alkynyl ester (e.g., ethynyl ester and propynyl ester);
aryl(lower)alkyl ester optionally having at least one suitable substituent, such as mono- (or di- or tri-)phenyl(lower)alkyl ester optionally having at least one suitable substituent, which is exemplified by benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenylethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester and 4-hydroxy-3,5-di-t-butylbenzyl ester;
aryl ester optionally having at least one suitable substituent, such as phenyl ester, 4-chlorophenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester and cumenyl ester;
cyclo(lower)alkyl ester (e.g., cyclohexyl ester);
phthalidyl ester; and the like.

When the above-mentioned substituents are substituted, the number of the substituents is preferably 1 to 4, unless particularly specified.

Preferable examples of the objective compound (I) is a compound of the formula (IA):



(IA)

wherein

R^2 is methyl;

R^3 is chlorine;

R^4 is (1) lower alkenyl optionally substituted by aryl, (2) aryl, (3) lower alkyl, or (4) heterocyclic group optionally substituted by halogen;

R^6 is (1) aryl, (2) heterocyclic group, (3) bromine, (4) halo(lower)alkyl, (5) lower alkylthio, (6) nitro, (7) lower alkenyl substituted by aryl, (8) lower alkynyl substituted by aryl, (9) lower alkoxy optionally substituted by cyclo(lower)alkyl or aryl, (10) lower alkyl or (11) amino optionally substituted by protected carboxy or lower alkyl; and

A is ethenylene

and a salt thereof.

Of the above-mentioned compounds (IA), a compound wherein R^4 is aryl or lower alkenyl optionally substituted by aryl, R^6 is bromine, lower alkenyl substituted by aryl, lower alkynyl substituted by aryl or lower alkoxy optionally substituted by cyclo(lower)alkyl and a salt thereof are particularly preferable.

Of the above-mentioned compounds (I), a compound wherein R^1 is heterocyclic group substituted by a substituent selected from the group consisting of (1) aryl, (2) heterocyclic group, (3) halogen, (4) halo(lower)alkyl, (5) lower alkylthio, (6) nitro, (7) lower alkenyl optionally substituted by aryl, (8) lower alkynyl optionally substituted by aryl, (9) lower alkoxy optionally substituted by cyclo(lower)alkyl or aryl, (10) aryloxy and (11) amino optionally substituted by protected carboxy or lower alkyl, and a salt thereof are particularly preferable.

Particularly preferable groups are as follows.

R^1 : 2-chloro-4-(2-furyl)phenyl, 2-chloro-4-(2-thienyl)phenyl, 2-chloro-4-(phenylethynyl)phenyl, 4-bromo-2-chlorophenyl, 3-chloro-4-biphenylyl, 2-chloro-4-(1-propoxy)phenyl, 2-chloro-4-(1-pentoxy)phenyl, 2-chloro-4-((cyclopentyl)methyloxy)phenyl, 2-chloro-4-((cyclohexyl)methyloxy)phenyl, 4-benzyloxy-2-chlorophenyl, 2-chloro-4-(methylthio)phenyl, 2-chloro-4-(trifluoromethyl)phenyl, 2-chloro-4-(phenoxymethyl)phenyl, 2-chloro-4-nitrophenyl, 2-chloro-4-((E)-2-phenylethenyl)phenyl, 1-bromo-2-naphthyl,

R^2 : methyl,

R^3 : chlorine,

R^4 : p-tolyl, (E)-2-phenylethenyl, pentyl, phenyl, 5-chloro-2-thienyl,

5-bromo-2-thienyl,

R^6 : 2-furyl, 2-thienyl, phenylethynyl, bromine, phenyl, 1-propoxy, 1-pentoxy, (cyclopentyl)methyloxy, (cyclohexyl)methyloxy, benzyloxy, methylthio, trifluoromethyl, phenoxymethyl, nitro, (E)-2-phenylethenyl,

A: methylene,

L: ethenylene.

Preferable objective compound (I) is exemplified by the following compounds.

(E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,

(2E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,

(E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,

(2E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,

(E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,

(2E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,

(E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,

(2E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,

(E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-N-(1-pentanesulfonyl)-2-propenamide,

(E)-N-benzenesulfonyl-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenamide,

(E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-N-((4-methylbenzene)sulfonyl)-2-propenamide,

(2E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,

(E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-N-(5-chloro-2-thienyl)sulfonyl)-2-propenamide,

(E)-N-(5-bromo-2-thienyl)sulfonyl-3-(4-chloro-1-(2-chloro-4-

phenylbenzyl)-2-methylimidazol-5-yl)-2-propenamide,
(E)-3-((4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-(1-pentanesulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)benzyl)-2-

methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide,
(E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide,
(2E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide.

The production methods of the objective compound (I) are explained in detail in the following.

Production Method 1:

The objective compound (I) and a salt thereof can be produced by reacting compound (II) or reactive derivative at carboxy thereof or a salt thereof with compound (III) or a salt thereof.

The salts of compound (II), reactive derivative at carboxyl group thereof and compound (III) are exemplified by those shown with regard to compound (I).

Preferable reactive derivative at carboxy of compound (II) is acid halide, acid anhydride such as intramolecular acid anhydride, intermolecular acid anhydride and mixed acid anhydride, active amide, active ester and the like. Preferable examples thereof include acid chloride, acid azide, mixed acid anhydride with acid such as substituted phosphoric acid (e.g., dialkylphosphinic acid, phenylphosphonic acid, diphenylphosphinic acid, dibenzylphosphinic acid and halogenated phosphoric acid), dialklphosphinic acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid (e.g., methanesulfonic acid), aliphatic carboxylic acid (e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid and trichloroacetic

acid), aromatic carboxylic acid (e.g., benzoic acid), and the like; symmetric acid anhydride; active amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; active ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichloro-phenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenylthio ester, p-cresylthio ester, carboxymethylthio ester, pyranyl ester, pyridyl ester, piperidyl ester and 8-quinolylthio ester); esters with N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-1H-pyridone, N-hydroxysuccinimide and 1-hydroxy-1H-benzotriazole); and the like. These reactive derivatives can be appropriately selected according to the kind of compound (II) to be used.

The reaction generally proceeds in a conventional solvent such as water, alcohol (e.g., methanol and ethanol), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide and pyridine, or in a solvent which does not adversely affect the reaction. These conventional solvents may be used alone or in combination.

When compound (II) is used in the form of a free acid or a salt thereof in this reaction, the reaction is preferably carried out in a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylamino-propyl)carbodiimide, N,N'-carbonylbis(2-methyl-imidazole), pentamethyleneketen-N-cyclohexylimine, diphenylketen-N-cyclohexylimine, ethoxyacetylene, 1-alkoxy-1-chloroethylene, trialkyl phosphite, ethyl polyphosphorate, isopropyl polyphosphorate, phosphorous oxychloride (phosphoryl chloride), trichlorophosphine, diphenylphosphonyl azide, diphenyl chlorophosphate, diphenylphosphinic acid chloride, thionyl chloride, oxaryl chloride, lower alkyl haloformate (e.g., methyl chloroformate and isopropyl chloroformate), triphenylphosphine, 2-ethyl-7-hydroxybenzoisoxazorium salt, intramolecular salt of 2-ethyl-5-(m-sulfophenyl)isoxazorium hydroxide, 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, and so-called

Vilsmeier reagent(prepared from N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, or phosphoryl chloride, and so on), and the like.

The reaction can be carried out in the presence of an inorganic or organic base such as alkali metal of bicarbonic acid, tri(lower)alkylamine, pyridine, 4-dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylaniline (e.g., N,N-dimethylaniline), N,N-di(lower)alkylbenzylamine, and the like.

The reaction temperature is not particularly limited, and the reaction is generally carried out under cooling to heating.

The aforementioned compounds can be converted to preferable salts as necessary by a conventional method (e.g., the method described in Example 85 to be mentioned later). All of them can be purified as necessary according to a conventional method for purifying an organic compound, such as recrystallization, column chromatography, thin-layer chromatography, high performance liquid chromatography and the like. The compound can be identified by NMR spectrometric analysis, mass spectrometric analysis, IR spectrometric analysis, elemental anlysis, melting point measurement and the like.

The compound of the present invention may have one or more chiral centers and includes enantiomers and diastereomers. Some compounds having alkenyl may be present as a cis or trans isomer. The present invention encompasses such mixtures and respective isomers.

The inventive compound and a salt thereof may be in the form of a solvate, which is also encompassed in the present invention. The solvate is preferably exemplified by hydrate and ethanolate.

The pharmaceutical data of compound (I) are shown in the following to demonstrate the utility of the objective compound (I).

Experimental Example 1

(blood sugar level depressing activity in dd/db mice)

Test compound

compound A:

(E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-N-((4-methylbenzene)sulfonyl)-2-propenamide (compound of Example 11)

Test animal

Female C57BL/KsJ-dbm db+/db+, C57BL/KsJ-dbm +m/+m (Jackson Laboratory) mice (5 weeks old) were purchased and subjected to the

test after 2-3 weeks of acclimating period.

Drug administration

The test drug was mixed with a powder diet (CE-2, Clea Japan, Inc.) in a mortar. In the case of administration in 100 mg/kg, the mixing proportion of the test drug to the diet was 0.1%, in the case of 30 mg/kg, the proportion was 0.03% and in the case of 10 mg/kg, the proportion was 0.01%. The diet was changed twice a week. The amount of the diet given and the amount left were recorded and the diet intake was calculated by determining the difference.

Test schedule

The female db/db mice were grouped according to body weight, blood sugar level and triglyceride concentration in blood. Then, the drug-mixed diet was given for 14 days, during which period the mice were 8 to 10 weeks of age. At day 7 and day 14 in the morning, blood was taken from supraorbital plexus venosus using a heparinized glass capillary tube (Chase Heparinized capillary tube), and centrifuged to give plasma fractions. The blood sugar value, triglyceride concentration in plasma and insulin concentration in plasma were measured at day 0 and day 14, and blood sugar value and triglyceride concentration in blood were measured at day 7. Body weight was measured at day 0, day 7 and day 14. After final blood sampling, the mice were slaughtered with CO_2 gas.

Measurement method

Blood sugar value was measured using 10-15 μl of plasma and in accord with glucose oxidase method (glucose CII-test Waco, Waco Pure Chemicals Co., Ltd.). The triglyceride concentration in plasma was measured using 10-15 μl of plasma and in accord with GPO-p-chlorophenol method (triglyceride G-test Waco) or GPO-DAOS method (triglyceride E-test Waco). The measurement was done promptly after blood sampling. The insulin concentration in plasma was measured using 20 μl of plasma (preservable at -20°C) and in accord with an antibody method (Phadesef Insulin RIA kit, Kabi Pharmacia).

Result

Using the difference between db/db mice control group and +/+ mice in blood sugar value and triglyceride concentration in plasma as 100%, the proportion (%) of decrease in the blood sugar value and triglyceride concentration in plasma of the group administered with the test drug was determined. The results are shown in Table 1.

Tabl 1

Test compound	Dose (mg/kg)	Blood sugar decrease (%)
Compound A	3.2	63

The compound (I) of the present invention can be used for therapeutic purposes in the form of a pharmaceutical preparation. This pharmaceutical preparation contains any one of the compounds (I) as an active ingredient in admixture with a pharmaceutically acceptable organic or inorganic excipient which is a solid, semi-solid or liquid and which is suitable for oral, parenteral or external (local) administration. Examples of the dosage form include capsules, tablets, sugar coating tablets, granules, suppositories, liquid, lotion, suspension, emulsion, ointment, gel and the like. When desired, these preparations may contain adjuvant auxiliary, auxiliary substance, stabilizer, moistening agent, emulsifier, buffering agent, and other conventional additives.

While the dose of the compound (I) varies depending on the age and symptom of patients, compound (I) is administered for the therapy of the above-mentioned diseases in an average single dose amount of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg or 1000 mg. In general, its daily dose is about 0.1 mg/patient to about 1000 mg/patient.

【Example】

The present invention is described in more detail by way of Preparation Examples and Examples.

Preparation Example 1-1

4,5-Dibromo-2-methylimidazole (4.91 g) was dissolved in N,N-dimethylformamide(50 ml), and 60% sodium hydride (901 mg) was added gradually under ice-cooling. After stirring at room temperature for 1 hour, 2-(trimethylsilyl)ethoxymethyl chloride (3.75 g) was gradually added dropwise under ice-cooling, and the mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and ethyl acetate was added to the residue. The reaction mixture was washed with saturated aqueous sodium hydrogencarbonate solution and brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column

chromatography (hexane/ethyl acetate=3/1) to give 4,5-dibromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)imidazole (7.6 g) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 0.00(9H, s), 0.92(2H, t, J=8Hz), 2.47(3H, s), 3.55(2H, t, J=8Hz), 5.24(2H, s).

Preparation Example 1-2

4,5-Dibromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-imidazole (29.2 g) was dissolved in tetrahydrofuran (250 ml), and 1.63N 1-butyl lithium/hexane solution (58.1 ml) was added dropwise over 20 min at from -55℃ to -60℃. The mixture was stirred at -60℃ for 30 min and N,N-dimethylformamide(58 g) was added dropwise at from -55℃ to -60℃. The mixture was stirred at room temperature for 1 hr. Saturated brine was added and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=3/1) to give 4-bromo-2-methyl-1-((2-(trimethylsilyl)-ethoxy)methyl)imidazole-5-carboxyaldehyde (18.5 g) as a pale-yellow oil.

^{1}H-NMR($CDCl_3$) : 0.00(9H, s), 0.91(2H, t, J=8Hz), 2.52(3H, s), 3.58(2H, t, J=8Hz), 5.70(2H, s), 9.71(1H, s).

Preparation Example 1-3

4-Bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-imidazole-5-carboxyaldehyde (18.5 g) was dissolved in ethanol (80 ml) and 6N hydrochlic acid (80 ml) was added. The mixture was refluxed under heating for 1 hr. The solvent was evaporated under reduced pressure and saturated aqueous sodium hydrogencarbonate solution was added under ice-cooling until the mixture assumed weak alkalinity. The precipitated crystals were collected by filtration, and the crystals were washed with methanol and heat-dried under reduced pressure to give 5-bromo-2-methylimidazole-4-carboxyaldehyde (9.17 g) as white crystals.

^{1}H-NMR($CDCl_3$) : 2.45(3H, s), 9.53(1H, s).

Preparation Example 1-4

5-Bromo-2-methylimidazole-4-carboxyaldehyde (400 mg) was dissolved in con. hydrochlic acid (6 ml), and the mixture was refluxed under heating for 24 hr. Saturated aqueous sodium hydrogencarbonate solution was added under ice-cooling until the mixture assumed weak

alkalinity and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution and then brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. Hexane was added to the residue and the crystals were collected by filtration to give 5-chloro-2-methylimidazole-4-carboxyaldehyde (222 mg) as yellow crystals.
^{1}H-NMR($CDCl_3$) : 2.45(3H, s), 9.58(1H, s).

Preparation Example 2

To a solution of 2-chloro-4-iodotoluene (7.59 g) in carbon tetrachloride (76 ml) were added N-bromosuccinimide (5.89 g) and 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (Wako V-70, 281 mg) at room temperature and the mixture was stirred at 55°C for 3.5 hr. The reaction mixture was allowed to cool to room temperature and thereto was added hexane (76 ml). Insoluble matter was filtered off. The filtrate was concentrated and the residue was again dissolved in hexane. The mixture washed successively with water, 5% aqueous sodium thiosulfate solution, saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 2-chloro-4-iodobenzyl bromide (8.45 g) as an oil.
^{1}H-NMR($CDCl_3$) : 4.52(2H, s), 7.16(1H, d, J=8Hz), 7.59(1H, dd, J=8 and 2Hz), 7.76(1H, d, J=2Hz).

Preparation Example 3-1

To a suspension of tetrakis(triphenylphosphine)palladium (213 mg) in toluene (7 ml) was added 2-chloro-4-iodotoluene (2.33 g) at room temperature. The mixture was stirred at room temperature for 30 min, and thereto were added a solution of phenylboronic acid (1.35 g) in EtOH (2 ml) and 2M aqueous sodium hydrogencarbonate solution (9.25 ml), and the mixture was refluxed under heating. After 3 hr, the reaction mixture was cooled and the organic layer was separated. The aqueous layer was extracted with hexane (4 ml). The organic layers were combined, washed with saturated aqueous sodium hydrogencarbonate solution (4 ml) and saturated brine (4 ml), and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated, and hexane (10 ml) and silica gel (4 g) were added to the residue (2.11 g). The mixture was stirred at room temperature for 1 hr. Silica gel was filtered off and the filtrate was concentrated to give 2-

chloro-4-phenyltoluene as a pale-brown oil (1.86 g, 99.4%).
^{1}H-NMR($CDCl_3$) : 2.40(3H, s), 7.2 3-7.60(8H, m).

Preparation Example 3-2

In the same manner as in the aforementioned Preparation Example 2, 2-chloro-4-phenylbenzyl bromide was obtained as colorless crystals (3.22 g) from 2-chloro-4-phenyltoluene (3.6 g).
^{1}H-NMR($CDCl_3$) : 4.64(2H, s), 7.35-7.63(8H, m).
m.p. 73-74°C.

Preparation Example 4-1

2-Chloro-4-iodotoluene(22.0 g) was dissolved in N,N-dimethylformamide (110 ml), and copper(I) iodide (49.8 g), ethyl chlorodifluoroacetate (37.8 g) and potassium fluoride (15.2 g) were added. The mixture was stirred at internal temperature of 116°C for 70 hr. The reaction mixture was filtered through celite. Water (11 ml) and diethyl ether (110 ml) were added to the filtrate under ice-cooling and the mixture was filtered through celite. The filtrate was separated and the aqueous layer was extracted again with diethyl ether (110 ml). The organic layers were combined and washed with saturated brine (110 ml), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 2-chloro-4-trifluoromethyltoluene (23.0 g) as a brown oil.
^{1}H-NMR($CDCl_3$) : 2.43(3H, s), 7.34(1H, d, J=8Hz), 7.42(1H, d, J=8Hz), 7.60(1H, s).

Preparation Example 4-2

In the same manner as in the aforementioned Preparation Example 2, 2-chloro-4-(trifluoromethyl)benzyl bromide (6.20 g) was obtained as a pale-yellow oil from 2-chloro-4-trifluoromethyltoluene (10.0 g).
^{1}H-NMR($CDCl_3$) : 4.59(2H, s), 7.52(1H, d, J=8Hz), 7.57(1H, d, J=8Hz), 7.67(1H, s).

Preparation Example 5-1

3-Chloro-4-methylphenol (2.00 g) was dissolved in N,N-dimethylformamide (10.0 ml), and potassium carbonate (2.91 g) and 1-propyl iodide (2.62 g) were added. The mixture was stirred at room temperature for 20 hr, and the reaction mixture was concentrated under reduced pressure. Water was added, and the mixture was extracted with AcOEt. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was applied to

silica gel column chromatography and eluted with hexane:ethyl acetate=5:1. The objective fraction was concentrated under reduced pressure to give 2-chloro-4-(1-propoxy)toluene (2.18 g) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 1.02(3H, t, J=7Hz), 1.72-1.85(2H, m), 2.29(3H, s), 3.88(2H, t, J=7Hz), 6.71(1H, dd, J=8, 2Hz), 6.90(1H, d, J=2Hz), 7.09(1H, d, J=8Hz).

Preparation Example 5-2

In the same manner as in the aforementioned Preparation Example 2, 2-chloro-4-(1-propoxy)benzyl bromide (2.26 g) was obtained as a pale-yellow oil from 2-chloro-4-(1-propoxy)toluene (2.14 g).

^{1}H-NMR($CDCl_3$) : 1.03(3H, t, J=7Hz), 1.75-1.87(2H, m), 3.90(2H, t, J=7Hz), 4.59(2H, s), 6.78(1H, dd, J=8, 2Hz), 6.93(1H, d, J=2Hz), 7.32(1H, d, J=8Hz).

Preparation Example 6-1

In the same manner as in the aforementioned Preparation Example 5-1, 2-chloro-4-(1-pentoxy)toluene (16.3 g) was obtained as a pale-brown oil from 2-chloro-4-methylphenol (10.0 g).

^{1}H-NMR($CDCl_3$) : 0.93(3H, t, J=6Hz), 1.40(4H, m), 1.76(2H, m), 2.29(2H, s), 3.90(2H, t, J=6Hz), 6.70(1H, dd, J=8, 2Hz), 6.90(1H, d, J=2Hz), 7.10(1H, d, J=8Hz).

Preparation Example 6-2

In the same manner as in the aforementioned Preparation Example 2, 2-chloro-4-(1-pentoxy)benzyl bromide (21.9 g) was obtained as a pale-yellow solid from 2-chloro-4-(1-pentoxy)toluene (16.2 g).

^{1}H-NMR($CDCl_3$) : 0.93(3H, t, J=6Hz), 1.40(4H, m), 1.76(2H, m), 3.93(2H, t, J=6Hz), 4.58(2H, s), 6.77(1H, dd, J=8, 2Hz), 6.92(1H, d, J=2Hz), 7.32(1H, d, J=8Hz).

Preparation Example 7-1

To a solution of 3-chloro-4-methylphenol (1.00 g) in N,N-dimethylformamide (8 ml) was added potassium carbonate powder (1.44 g) and the mixture was heated to 80°C. Thereto was added cyclopentylmethyl methanesulfonate (1.57 g) and the mixture was stirred at 120°C for 3 hr. The reaction mixture was cooled to room temperature. Water was added and the mixture was extracted 3 times with hexane. The organic layers were combined and washed successively with 1N aqueous sodium hydroxide solution, water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was

evaporated and the residue was purified by column chromatography (silica gel, hexane) to give 2-chloro-4-((cyclopentyl)methyloxy)-toluene (1.46 g) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 1.22-1.93(8H, m), 2.29(3H, s), 2.34(1H, sept, J=7Hz), 3.78(2H, d, J=7Hz), 6.71(1H, dd, J=8 and 2Hz), 6.91(1H, d, J=2Hz), 7.09(1H, d, J=8Hz).

Preparation Example 7-2

In the same manner as in the aforementioned Preparation Example 2, 2-chloro-4-((cyclopentyl)methyloxy)benzyl bromide (2.06 g) was obtained as an oil from 2-chloro-4-((cyclopentyl)methyloxy)toluene (1.45 g).

^{1}H-NMR($CDCl_3$) : 1.23-1.92(8H, m), 2.34(1H, sept, J=7Hz), 3.81(2H, d, J=7Hz), 4.59(2H, s), 6.78(1H, dd, J=9 and 2Hz), 6.93(1H, d, J=2Hz), 7.32(1H, d, J=9Hz).

Preparation Example 8-1

In the same manner as in the aforementioned Preparation Example 5-1, 2-chloro-4-((cyclohexyl)methyloxy)toluene (1.41 g) was obtained as colorless crystals from 3-chloro-4-methylphenol (926 mg).

^{1}H-NMR($CDCl_3$) : 0.95-1.40(5H), 1.64-1.90(6H), 2.29(3H, s), 3.70(2H, d, J=6Hz), 6.70(1H, dd, J=8, 2Hz), 6.89(1H, d, J=2Hz), 7.08(1H, d, J=8Hz).

Preparation Example 8-2

In the same manner as in the aforementioned Preparation Example 2, 2-chloro-4-((cyclohexyl)methyloxy)benzyl bromide (1.35 g) was obtained as a pale-yellow solid from 2-chloro-4-((cyclohexyl)methyloxy)toluene (1.00 g).

^{1}H-NMR($CDCl_3$) : 0.94-1.40(5H), 1.63-1.94(6H), 3.73(2H, d, J=6Hz), 4.59(2H, s), 6.79(1H, dd, J=8, 2Hz), 6.93(1H, d, J=2Hz), 7.32(1H, d, J=8Hz).

Preparation Example 9

To a solution of 4-bromo-2-chlorobenzyl alcohol (3.56 g) and anhydrous triethylamine (3 ml) in anhydrous dichloromethane (36 ml) was added dropwise methanesulfonyl chloride (1.4 ml) under ice-cooling in a nitrogen atmosphere. The mixture was stirred for 1 hr, and the reaction mixture was washed with water, saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The filtrate was concentrated to give 4-bromo-2-chloro-1-((methanesulfonyloxy)methyl)benzene as a pale-

brown solid (4.77 g).

^{1}H-NMR($CDCl_3$) : 3.03(3H, s), 5.29(2H, s), 7.37(1H, d, J=8Hz), 7.47(1H, dd, J=8, 1Hz), 7.60(1H, d, J=1Hz).

Mass(ESI) : m/z 298(M-1).

Preparation Example 10-1

To a solution of methyl 4-bromo-2-chlorobenzoate (1.25 g) in N,N-dimethylformamide (10 ml) was added sodium thiomethoxide (459 mg) under ice-cooling and the mixture was stirred for 2 hr. To the reaction mixture was added 1N hydrochlic acid and the resulting product was extracted 3 times with ether. The organic layers were combined, washed successively with water and saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was applied to silica gel column chromatography (hexane/ethyl acetate=10/1) to give methyl 2-chloro-4-(methylthio)benzoate (835 mg) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 2.49(3H, s), 3.90(3H, s), 7.11(1H, d, J=8Hz), 7.23(1H, s), 7.78(1H, d, J=8Hz).

Preparation Example 10-2

To a suspension of aluminum lithium hydride (139 mg) in tetrahydrofuran (8 ml) was added dropwise methyl 2-chloro-4-(methylthio)benzoate (806 mg) under ice-cooling, and the mixture was stirred for 1 hr. The reaction mixture was diluted with ether and 1N hydrochlic acid (10 ml) was added dropwise. The resulting product was extracted 3 times with ether. The organic layers were combined and washed successively with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 2-chloro-4-(methylthio)benzyl alcohol (725 mg) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 1.92(1H, br t, J=7Hz), 2.48(3H, s), 4.73(2H, d, J=7Hz), 7.15(1H, d, J=8Hz), 7.23(1H, s), 7.37(1H, d, J =8Hz).

Preparation Example 10-3

In the same manner as in the aforementioned Preparation Example 9, 2-chloro-1-((methanesulfonyloxy)methyl)-4-(methylthio)benzene (1.02 g) was obtained as a colorless oil from 2-chloro-4-(methylthio)benzyl alcohol (687 mg).

^{1}H-NMR($CDCl_3$) : 2.48(3H, s), 3.00(3H, s), 5.30(2H, s), 7.15(1H, dd, J=8 and 2Hz), 7.26(1H, d, J=2Hz), 7.38(1H, d, J=8Hz).

Preparation Example 11

In the same manner as in the aforementioned Preparation Example 9, 2-chloro-1-((methanesulfonyloxy)methyl)-4-nitrobenzene (3.56 g) was obtained as brown crystals from 2-chloro-4-nitrobenzyl alcohol (2.5 g).

^{1}H-NMR($CDCl_3$) : 3.12(3H, s), 5.40(2H, s), 7.73(1H, d, J=8Hz), 8.18(1H, dd, J=2,8Hz), 8.79(1H, d, J=2Hz).

Preparation Example 12-1

4-Amino-2-chlorobenzoic acid (10.01 g) was homogeneously dissolved in 12.5% sulfuric acid (400 ml) by heating to 70°C and ice-cooled. To this suspension was added dropwise aqueous sodium nitrite solution (4.24 g/12 ml of water) at not more than 8°C over 5 min. After 5 min, this solution was gradually poured into water (500 ml) at 80°C, upon which the solution foamed vigorously and turned into a red solution. The reaction mixture was stirred at 80°C for 1 hr. After allowing to cool, the resulting product was extracted 3 times with ether. The organic layers were combined and washed successively with dilute hydrochlic acid, water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated and a small amount of diisopropyl ether was added to the residue to allow for crystallization to give 2-chloro-4-hydroxybenzoic acid (6.32 g) as an orange powder.

^{1}H-NMR(DMSO-d_6) : 6.79(1H, dd, J=8 and 2Hz), 6.88(1H, d, J=2Hz), 7.77(1H, d, J=8Hz).

Mass(ESI) : m/e 171(M-H)-.

Preparation Example 12-2

To a solution of 2-chloro-4-hydroxybenzoic acid (695 mg) in N,N-dimethylformamide (3.5 ml) were added potassium carbonate (1.67 g) and benzyl bromide (1.73 g) and the mixture was stirred at room temperature for 14 hr. To the reaction mixture was added 1N hydrochlic acid and the resulting product was extracted 3 times with ether. The organic layers were combined and washed successively with water, saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated and recrystallized from diisopropyl ether/hexane to give benzyl 4-benzyloxy-2-chlorobenzoate (1.13 g) as a pale-yellow powder.

^{1}H-NMR($CDCl_3$) : 5.09(2H, s), 5.32(2H, s), 6.87(1H, dd, J=8 and 2Hz), 7.05(1H, d, J=2Hz), 7.29-7.50(10H, m), 7.91(1H, d, J=8Hz).

Mass(ESI) : m/e 353(M+H)+.

Preparation Example 12-3

To benzyl 4-benzyloxy-2-chlorobenzoate (1.12 g) were added ethanol (8.8 ml), 1,4-dioxane (2.2 ml) and 1N aqueous sodium hydroxide solution (4.7 ml) and the mixture was stirred at 70°C for 1.5 hr. The solvent was evaporated and water was added to the residue for dissolution, which was washed with ether. This aqueous layer was acidified with 1N hydrochlic acid and the precipitate was collected by filtration to give 4-benzyloxy-2-chlorobenzoic acid (810 mg) as a pale-yellow powder.

^{1}H-NMR(DMSO-d_6) : 5.20(2H, s), 7.06(1H, dd, J=8 and 2Hz), 7.18(1H, d, J=2Hz), 7.29-7.50(5H, m), 7.82(1H, d, J=8Hz).

Mass(ESI) : m/e 261(M-H)-.

Preparation Example 12-4

To a solution of 4-benzyloxy-2-chlorobenzoic acid (788 mg) in tetrahydrofuran (7.9 ml) was added dropwise borane·dimethylsulfide complex (10.0M, 0.6 ml) at room temperature under a nitrogen atmosphere and the mixture was refluxed under heating for 2.5 hr. The reaction mixture was allowed to cool to room temperature, and 1N hydrochlic acid (1.5 ml) was carefully added dropwise. The mixture was stirred for 30 min. To the reaction mixture was added water and the resulting produce was extracted 3 times with ethyl acetate. The organic layers were combined, washed successively with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 4-benzyloxy-2-chlorobenzyl alcohol (778 mg) as a white powder.

^{1}H-NMR($CDCl_3$) : 1.83(1H, br t, J=7Hz), 4.70(2H, d, J=7Hz), 5.05(2H, s), 6 .88(1H, dd, J=8 and 2Hz), 7.01(1H, d, J=2Hz), 7.28-7.46(6H, m).

Preparation Example 12-5

In the same manner as in the aforementioned Preparation Example 9, 4-benzyloxy-2-chlorobenzyl chloride (639 mg) was obtained as a colorless oil from 4-benzyloxy-2-chlorobenzyl alcohol (523 mg).

^{1}H-NMR($CDCl_3$) : 4.67(2H, s), 5.05(2H, s), 6.87(1H, dd, J=8 and 2Hz), 7.02(1H, d, J= 2Hz), 7.28-7.44(6H, m).

Preparation Example 13-1

To a solution of 4-bromo-2-chlorobenzyl alcohol (14.48 g) in N,N-dimethylformamide (72 ml) were added imidazole (5.34 g) and tert-butylchlorodiphenylsilane (19.8 g) under ice-cooling, and the

mixture was stirred for 1 hr. Water was added to the reaction mixture and the resulting product was extracted twice with hexane. The organic layers were combined, washed successively with water, saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was applied to silica gel column chromatography (hexane) to give 4-bromo-1-((tert-butyldiphenylsiloxy)methyl)-2-chlorobenzene (29.22 g) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 1.10(9H, s), 4.75(2H, s), 7.32-7.50(8H, m), 7.55-7.72(5H, m).

Preparation Example 13-2

To a solution of 4-bromo-1-((tert-butyldiphenylsiloxy)-methyl)-2-chlorobenzene (8.65 g) in tetrahydrofuran (22 ml) was added 1-butyl lithium/hexane solution (1.54M, 13.5 ml) at -75°C in a nitrogen atmosphere, and the mixture was stirred for 15 min. The reaction mixture was once heated to 10°C and again cooled to -75°C and 1-formyl piperidine (2.55 g) was added dropwise over 10 min. The reaction mixture was heated to room temperature over 3 hr. To the reaction mixture was added aqueous ammonium chloride solution and the resulting product was extracted twice with hexane. The organic layers were combined, washed successively with dilute hydrochlic acid, saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was applied to silica gel column chromatography (hexane/ethyl acetate=40/1) to give 4-((tert-butyldiphenylsiloxy)methyl)-3-chlorobenzaldehyde (3.26 g) as a pale-yellow oil.

^{1}H-NMR($CDCl_3$) : 1.14(9H, s), 4.87(2H, s), 7.33-7.51(6H, m), 7.63-7.75(4H, m), 7.81(1H, d, J=2Hz), 7.84(1H, dd, J=8 and 2Hz), 7.97(1H, d, J=8Hz), 9.97(1H, s).

Preparation Example 13-3

To a suspension of 4-((tert-butyldiphenylsiloxy)methyl)-3-chlorobenzaldehyde (3.24 g) in ethanol (32 ml) was added sodium borohydride (149 mg) under ice-cooling and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated to about half amount. Water was added and the resulting product was extracted twice with diisopropyl ether. The organic layers were combined, washed successively with saturated aqueous sodium

hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=5/1) to give 4-((tert-butyldiphenylsiloxy)methyl)-3-chlorobenzyl alcohol (3.08 g) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 1.12(9H, s), 1.70(1H, br t, J=5Hz), 4.69(2H, d, J=5Hz), 4.83(2H, s), 7.27-7.50(8H, m), 7.65-7.78(5H, m).

Preparation Example 13-4

In the same manner as in the aforementioned Preparation Example 9, 1-((tert-butyldiphenylsiloxy)methyl)-2-chloro-4-((methanesulfonyloxy)methyl)benzene (3.80 g) was obtained as a colorless oil from 4-((tert-butyldiphenylsiloxy)methyl)-3-chlorobenzyl alcohol (3.05 g).

^{1}H-NMR($CDCl_3$) : 1.12(9H, s), 2.97(3H, s), 4.83(2H, s), 5.21(2H, s), 7.33-7.50(8H, m), 7.63-7.75(4H, m), 7.77-7.83(1H, m).

Preparation Example 13-5

To a solution of phenol (969 mg) in N,N-dimethylformamide (27 ml) was added potassium carbonate powder (1.92 g) and the mixture was stirred at room temperature for 5 min. 1-((tert-Butyldiphenylsiloxy)methyl)-2-chloro-4-((methanesulfonyloxy)methyl)benzene (3.39 g) was added and the mixture was stirred at 100°C for 3 hr. The reaction mixture was allowed to cool to room temperature. Water was added and the mixture was extracted twice with hexane. The organic layers were combined, washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate=50/1) to give 1-((tert-butyldiphenylsiloxy)methyl)-2-chloro-4-(phenoxymethyl)benzene (2.65 g) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 1.12(9H, s), 4.83(2H, s), 5.04(2H, s), 6.93-7.04(3H, m), 7.25-7.50(10H, m), 7.65-7.73(4H, m), 7.73-7.80(1H, m).

Preparation Example 13-6

To a solution of 1-((tert-butyldiphenylsiloxy)methyl)-2-chloro-4-(phenoxymethyl)benzene (2.84 g) in tetrahydrofuran (14 ml) was added ammonium tetrabutylfluoride/tetrahydrofuran solution (1.0 M, 7.0 ml) under ice-cooling and the mixture was stirred for 1.5 hr. Water was added to the reaction mixture and the resulting product was extracted twice with ethyl acetate. The organic layers were combined,

washed successively with 1N hydrochlic acid, saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=5/1) to give 2-chloro-4-(phenoxymethyl)benzyl alcohol (1.38 g) as a white powder.

^{1}H-NMR($CDCl_3$) : 1.92(1H, br t, J=6Hz), 4.79(2H, d, J=6Hz), 5.05(2H, s), 6.8 8-7.06(3H, m), 7.23-7.40(3H, m), 7.42-7.57(2H, m).

Preparation Example 13-7

In the same manner as in the aforementioned Preparation Example 9, 2-chloro-1-((methanesulfonyloxy)methyl)-4-(phenoxymethyl)-benzene (1.83 g) was obtained as an oil from 2-chloro-4-(phenoxymethyl)benzyl alcohol (1.36 g).

^{1}H-NMR($CDCl_3$) : 3.03(3H, s), 5.07(2H, s), 5.35(2H, s), 6.91-7.04(3H, m), 7. 25-7.42(3H, m), 7.44-7.67(2H, m).

Preparation Example 14-1

In the same manner as in the aforementioned Preparation Example 12-4, 3-chloro-4-methylbenzyl alcohol (23.0 g) was obtained as a colorless oil from 3-chloro-4-methylbenzoic acid (25.0 g).

^{1}H-NMR($CDCl_3$) :2.36(3H, s), 4.65(2H, s), 7.14(1H, d, J=8Hz), 7.23(1H, d, J=8Hz), 7.36(1H, s).

Preparation Example 14-2

To a solution of 3-chloro-4-methylbenzyl alcohol (2.00 g) and triethylamine (8.9 ml) in dimethyl sulfoxide (10 ml) was added sulfur trioxide - pyridine complex (4.47 g) under water-cooling. The mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into ice water and the mixture was extracted with ether. The organic layer was washed with 1N hydrochlic acid, saturated brine and saturated aqueous sodium hydrogencarbonate solution and dried over magnesium sulfate. The residue was concentrated to dryness under reduced pressure to give 3-chloro-4-methylbenzaldehyde (1.40 g) as a pale-yellow oil.

^{1}H-NMR($CDCl_3$) :2.46(3H, s), 4.65(2H, s), 7.40(1H, d, J=8Hz), 7.68(1H, d, J=8Hz), 9.92(1H, s).

Preparation Example 14-3

In the same manner as in Preparation Example 15-2 to be mentioned later, (E)-2-chloro-4-(2-phenylethenyl)toluene (1.55 g) was obtained as a white powder from 3-chloro-4-methylbenzaldehyde (1.40 g) and

diethyl benzylphosphonate (2.27 g).

^{1}H-NMR($CDCl_3$) :2.38(3H, s), 7.00(1H, d, J=16Hz), 7.08(1H, d, J=1 6Hz), 7.18-7.53(8H).

Preparation Example 14-4

In the same manner as in the aforementioned Preparation Example 2, (E)-2-chloro-4-(2-phenylethenyl)benzyl bromide (309 mg) was obtained as a white powder from (E)-2-chloro-4-(2-phenylethenyl)toluene (1.35 g).

^{1}H-NMR($CDCl_3$) :4.61(2H, s), 7.01(1H, d, J=16Hz), 7.14(1H, d, J=16Hz), 7.24-7.57(8H).

Preparation Example 15-1

To a solution of 5-chloro-2-methylimidazole-4-carboxyaldehyde (433 mg) in N,N-dimethylformamide (4.3 ml) were added potassium carbonate powder (616 mg) and 2-chloro-4-iodobenzyl bromide (1.2 equivalents) under ice-cooling and the mixture was stirred at room temperature for 2.5 hr. To the reaction mixture were added water and saturated brine, and the resulting product was extracted twice with ethyl acetate. The organic layers were combined, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated and purified by silica gel column chromatography (hexane/ethyl acetate=5/1) to give 4-chloro-1-(2-chloro-4-iodobenzyl)-2-methylimidazole-5-carboxyaldehyde (1.01 g) as a white powder.

^{1}H-NMR($CDCl_3$) : 2.33(3H, s), 5.56(2H, s), 6.21(1H, d, J=8Hz), 7.50(1H, dd, J=8 and 2Hz), 7.78(1H, d, J=2Hz), 9.75(1H, s).

Mass(ESI) : m/e 395(M+H)+.

Preparation Example 15-2

To a solution of 4-chloro-1-(2-chloro-4-iodobenzyl)-2-methylimidazole 5-carboxyaldehyde (1.01 g) in tetrahydrofuran (10 ml)was added methyl (triphenylphosphoranylidene)acetate (1.27 g) and the mixture was refluxed under heating for 4 hr. The solvent was evaporated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=3/1) to give methyl (E)-3-(4-chloro-1-(2-chloro-4-iodobenzyl)-2-methylimidazol-5-yl)-2-propenate (974 mg) as a white powder.

^{1}H-NMR($CDCl_3$) : 2.33(3H, s), 3.75(3H, s), 5.15(2H, s), 6 .17(1H, d, J=8Hz), 6.49(1H, d, J=16Hz), 7.28(1H, d, J=16Hz), 7.53(1H, dd, J=8 and 2Hz), 7.81(1H, d, J=2Hz).

Mass(ESI) : m/e 451(M+H)+.

Preparation Example 15-3

A mixture of tetrakis(triphenylphosphine)palladiium(0) (89 mg), methyl (E)-3-(4-chloro-1-(2-chloro-4-iodobenzyl)-2-methylimidazol-5-yl)-2-propenate (350 mg), 2-furyl boronic acid (135 mg), potassium carbonate powder (321 mg) and N,N-dimethylformamide (3.5 ml) was stirred under a nitrogen atmosphere at 80°C for 4 hr. The reaction mixture was allowed to cool to room temperature and water was added. The precipitate was collected by filtration. The precipitate was dissolved in chloroform, washed successively with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform/ethyl acetate=10/1) to give methyl (E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-2-propenate (336 mg) as a pale-yellow powder.

^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 3.74(3H, s), 5.22(2H, s), 6.44-6.50(2H, m), 6.50(1H, d, J=16Hz), 6.68(1H, d, J=3Hz), 7.34(1H, d, J=16Hz), 7.43-7.50(2H, m), 7.76(1H, d, J=2Hz).

Mass(ESI) : m/e 391(M+H)+.

Preparation Example 15-4

To a suspension of methyl (E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-2-propenate (319 mg) in 1,4-dioxane (1.6 ml) was added 1N aqueous sodium hydroxide solution (1.2 ml) and the mixture was stirred at 50°C for 1 hr. The reaction mixture was ice-cooled and 1N hydrochlic acid (1.2 ml) was added dropwise to neutralize the mixture. The resulting product was extracted 3 times with chloroform-methanol (4/1). The organic layers were combined, washed with saturated brine, and dried over magnesium sulfate. The solvent was evaporated to give (E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (310 mg) as a gray white powder.

^{1}H-NMR(DMSO-d_6) : 2.34(3H, s), 5.41(2H, s), 6.26(1H, d, J=16Hz), 6.58(1H, d, J=8Hz), 6.62(1H, dd, J=3 and 2Hz), 7.09(1H, d, J=3Hz), 7.22(1H, d, J=16Hz), 7.62(1H, dd, J=8 and 2Hz), 7.79(1H, d, J=2Hz), 7.88(1H, d, J=2Hz).

Mass(ESI) : m/e 375(M-H)-.

Preparation Example 16-1

In the same manner as in the aforementioned Preparation Example 15-3, methyl (E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-2-propenate was obtained as a yellow oil (331 mg) from methyl (E)-3-(4-chloro-1-(2-chloro-4-iodobenzyl)-2-methylimidazol-5-yl)-2-propenate (360 mg).

^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 3.74(3H, s), 5.23(2H, s), 6.47(1H, d, J=8Hz), 6.51(1H, d, J=16Hz), 7.07-7.11(1H, m), 7.29-7.38(3H, m), 7.41(1H, dd, J=2, 8Hz), 7.69(1H, d, J=2Hz).

Mass(ESI) : m/z 407(M+1).

Preparation Example 16-2

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid was obtained as pale-yellow crystals (231 mg) from methyl (E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-2-propenate (281 mg).

^{1}H-NMR(DMSO-d_6) : 2.34(3H, s), 5.42(2H, s), 6.27(1H, d, J=16Hz), 6.55(1H, d, J=8Hz), 7.12-7.19(1H, m), 7.25(1H, d, J=16Hz), 7.52-7.62(3H, m), 7.87(1H, d, J=2Hz).

Mass(ESI) : m/z 391(M-1).

Preparation Example 17-1

To a mixture of methyl (E)-3-(4-chloro-1-(2-chloro-4-iodobenzyl)-2-methylimidazol-5-yl)-2-propenate (360 mg), dichlorobis(triphenylphosphine)palladium(II) (28 mg) and copper iodide (7.6 mg) was added a solution of phenylacetylene (326 mg) in diisopropylamine (20 ml) in a nitrogen atmosphere and the mixture was refluxed under heating for 5 hr. The reaction mixture was allowed to cool. Water was added and the mixture was extracted twice with chloroform. The organic layers were combined, washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. The residue was filtrated under reduced pressure and concentrated to give a crude product. The product was applied to flash silica gel column chromatography (silica gel 10 g) to give methyl (E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-2-propenate as brown amorphous (331 mg) from the eluted fraction of hexane/ethyl acetate=5/1 - 1-1.

^{1}H-NMR($CDCl_3$) : 2.35(3H, s), 3.75(3H, s), 5.23(2H, s), 6.45(1H, d,

J=8Hz), 6.50(1H, d, J=16Hz), 7.27-7.40(5H, m), 7.48-7.56(2H, m), 7.63(1H, s).

Mass(ESI) : m/z 425(M+1).

Preparation Example 17-2

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid was obtained as pale-ocher crystals (283 mg) from methyl (E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-2-propenate (413 mg).

^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 5.23(2H, s), 6.45(1H, d, J=8Hz), 6.48(1H, d, J=16Hz), 7.32-7.41(5H, m), 7.48-7.55(2H, m), 7.64(1H, d, J=2Hz).

Mass(ESI) : m/z 409(M-1).

Preparation Example 18-1

In the same manner as in the aforementioned Preparation Example 15-1, 1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazole-5-carboxyaldehyde (430 mg) was obtained as pale-yellow crystals from 4-chloro-2-methylimidazole-5-carboxyaldehyde (200 mg) and 4-bromo-2-chloro-1-((methanesulfonyloxy)methyl)benzene (456 mg).

^{1}H-NMR($CDCl_3$) : 2.33(3H, s), 5.56(2H, s), 6.38(1H, d, J=8Hz), 7.31(1H, dd, J=8, 2Hz), 7.60(1H, d, J=2Hz), 9.75(1H, s).

Preparation Example 18-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenate (372 mg) was obtained as colorless crystals from 1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazole 5-carboxyaldehyde (394 mg) and methyl (triphenylphosphoranylidene)acetate (606 mg).

^{1}H-NMR($CDCl_3$) : 2.33(3H, s), 3.75(3H, s), 5.16(2H, s), 6.33(1H, d, J=8Hz), 6.50(1H, d, J=15Hz), 7.26(1H, d, J=2Hz), 7.34(1H, dd, J=8, 2Hz), 7.63(1H, d, J=2Hz).

Preparation Example 18-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenic acid (338 mg) was obtained as pale-yellow crystals from methyl (E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenate (355 mg).

^{1}H-NMR(DMSO-d_6) : 2.31(3H, s), 5.38(2H, s), 6.26(1H, d, J=15Hz), 6.45(1H, d, J=8Hz), 7.21(1H, d, J=15Hz), 7.53(1H, dd, J=8 , 2Hz), 7.87(1H, d, J=2Hz).

Preparation Example 19-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazole-5-carboxyaldehyde (1.23 g) was obtained as a colorless oil from 5-chloro-2-methylimidazole-4-carboxyaldehyde (600 mg) and 2-chloro-4-phenylbenzyl bromide (1.4 g).

^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 5.67(2H,s), 6.56(1H, d, J=8Hz), 7.35-7.55(6H), 7.65(1H, s), 9.80(1H, s).

Preparation Example 19-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenate (1.13 g) was obtained as a white powder from 4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazole-5-carboxyaldehyde (1.23 g).

^{1}H-NMR($CDCl_3$) : 2.37(3H, s), 3.74(3H , s), 5.25(2H,s), 6.46-6.57(2H), 7.30-7.55(7H), 7.68(1H, s).

Preparation Example 19-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenic acid (1.18 g) was obtained as a white powder from methyl (E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenate (1.35 g).

^{1}H-NMR(DMSO-d_6) : 2.35(3H, s), 5.45(2H,s), 6.30(1H, d, J=16Hz), 6.58(1H, d, J=8Hz), 7.25(1H, d, J=16Hz), 7.36-7.52(3H), 7.62(1H, d, J=8Hz), 7.69(2H, d, J=8Hz), 7.86(1H, s).

Preparation Example 20-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazole-5-carboxyaldehyde (376 mg) was obtained as pale-yellow crystals from 4-chloro-2-methylimidazole-5-carboxyaldehyde (200 mg) and 2-chloro-4-(1-propoxy)benzyl bromide (474 mg).

^{1}H-NMR($CDCl_3$) : 1.02(3H, t, J=7Hz), 1.73-1.85(2H, m), 2.32(3H, s), 3.87(2H, t, J=7Hz), 5.57(2H, s), 6.46(1H, d, J=8Hz), 6.70(1H, dd, J=8, 2Hz), 6.96(1H, d, J=2Hz), 9. 77(1H, s).

Preparation Example 20-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-2-propenate (348 mg) was obtained as colorless crystals from 4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazole-5-carboxyaldehyde (356 mg) and methyl (triphenylphosphoranylidene)acetate (546 mg).

^{1}H-NMR($CDCl_3$) : 1.02(3H, t, J =7Hz), 1.74-1.85(2H, m), 2.34(3H, s), 3.75(3H, s), 3.89(2H, t, J=7Hz), 5.15(2H, s), 6.37(1H, d, J=8Hz), 6.49(1H, d, J=15Hz), 6.71(1H, dd, J=8, 2Hz), 6.99(1H, d, J=2Hz), 7.34(1H, d, J=15Hz).

Preparation Example 20-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (305 mg) was obtained as colorless crystals from methyl (E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-2-propenate (332 mg).

^{1}H-NMR(DMSO-d_6) : 0.95(3H, t, J=7Hz), 1.64-1.75(2H, m), 2.32(3H, s), 3.92(2H, t, J=7Hz), 5.31(2H, s), 6.25(1H, d, J=15Hz), 6.44(1H, d, J=8Hz), 6.88(1H, dd, J=8, 2Hz), 7.13(1H, d, J=2Hz), 7.23(1H, d, J=15Hz).

Preparation Example 21-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-[2-chloro-4-(1-pentoxy)benzyl]-2-methylimidazole-5-carboxyaldehyde (460 mg) was obtained as a pale-yellow oil from 5-chloro-2-methylimidazole-4-carboxyaldehyde (200 mg) and 2-chloro-4-(1-pentoxy)benzyl bromide (378 mg).

^{1}H-NMR($CDCl_3$) : 0.93(3H, t, J=6Hz), 1.40(4H, m), 1.76(2H, m), 2.32(3H, s), 3.90(2H, t, J=6Hz), 5.57(2H, s), 6.45(1H, d, J=8Hz), 6.70(1H, dd, J=8, 2Hz), 6.95(1H, d, J=2Hz), 9.76(1H, s).

Preparation Example 21-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-2-propenate was obtained as a milky white solid (427 mg) from 4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazole-5-carboxyaldehyde (439 mg).

^{1}H-NMR($CDCl_3$) : 0.93(3H, t, J=7Hz), 1.32-1.49(4H, m), 1.71-1.83(2H, m), 2.34(3H, s), 3.75(3H, s), 3.92(2H, t, J=7Hz), 5. 15(2H, s), 6.37(1H,

d, J=8Hz), 6.49(1H, d, J=16Hz), 6.70(1H, dd, J=2, 8Hz), 6.99(1H, d, J=2Hz), 7.34(1H, d, J=16Hz).

Mass(ESI) : m/z 411(M+1).

Preparation Example 21-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid was obtained as thin yellow crystals (370 mg) from methyl (E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-2-propenate (403 mg).

^{1}H-NMR($CDCl_3$) : 0.92(3H, t, J=7Hz), 1.30-1.50(4H, m), 1.70-1.83(2H, m), 2.36(3H, s), 3.92(2H, t, J=7Hz), 5.16(2H, s), 6.38(1H, d, J=8Hz), 6.47(1H, d, J=16Hz), 6.71(1 H, dd, J=2, 8Hz), 6.99(1H, d, J=2Hz), 7.40(1H, d, J=16Hz).

Mass(ESI) : m/z 395(M-1).

Preparation Example 22-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)benzyl)-2-methylimidazole-5-carboxyaldehyde (608 mg) was obtained as a colorless oil from 5-chloro-2-methylimidazole-4-carboxyaldehyde (300 mg) and 2-chloro-4-((cyclopentyl)methyloxy)benzyl bromide (764 mg).

^{1}H-NMR($CDCl_3$) : 1.22-1.92(8H, m), 2.32(3H, s), 2.33(1H, sept, J=7Hz), 3.78(2H, d, J=7Hz), 5.57(2H, s), 6.45(1H, d, J=8Hz), 6.70(1H, dd, J=9 and 2Hz), 6.96(1H, d, J=2Hz), 9.77(1H, s).

Mass(ESI) : m/e 367(M+H)+.

Preparation Example 22-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)-methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenate (563 mg) was obtained as a white powder from 4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)benzyl)-2-methylimidazole-5-carboxyaldehyde (577 mg) and methyl (triphenylphosphoranylidene)acetate (788 mg).

^{1}H-NMR($CDCl_3$) : 1.24-1.92(8H, m), 2.34(3H, s), 2.34(1H, sept, J=7Hz), 3.74(3H, s), 3.79(2H, d, J=7Hz), 5.15(2H, s), 6.37(1H, d, J=8Hz), 6.49(1H, d, J=16Hz), 6.71(1H, dd, J=8 and 3Hz), 6.99(1H, d, J=3Hz), 7.34(1H, d, J=16Hz).

Mass(ESI) : m/e 423(M+H)+.

Preparation Example 22-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-2-propenic acid (532 mg) was obtained as a white powder from methyl (E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenate (535 mg).

^{1}H-NMR($CDCl_3$) : 1.23-1.92(8H, m), 2.33(1H, sept, J=7Hz), 2.35(3H, s), 3.79(2H, d, J=7Hz), 5 .15(2H, s), 6.37(1H, d, J=8Hz), 6.46(1H, d, J=16Hz), 6.71(1H, dd, J=8 and 2Hz), 6.99(1H, d, J=2Hz), 7.40(1H, d, J=16Hz).

Mass(ESI) : m/e 407(M-H)-.

Preparation Example 23-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)benzyl)-2-methylimidazole-5-carboxyaldehyde was obtained as a yellow oil (410 mg) from 5-chloro-2-methylimidazole-4-carboxyaldehyde (200 mg) and 2-chloro-4-((cyclohexyl)methyloxy)benzyl bromide (659 mg).

^{1}H-NMR($CDCl_3$) : 0.95-1.10(2H, m), 1.15-1.39(4H, m), 1.62-1.89(5H, m), 2.32(3H, s), 3.70(2H, d, J=7Hz), 5.57(2H, s), 6.45(1H, d, J=8Hz), 6.69(1H, dd, J=2, 8Hz), 6.95(1H, d , J=2Hz), 9.76(1H, s).

Mass(ESI) : m/z 381(M+1).

Preparation Example 23-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)-methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenate was obtained as a yellow oil (419 mg) from 4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)benzyl)-2-methylimidazole-5-carboxyaldehyde (405 mg).

^{1}H-NMR($CDCl_3$) : 0.95-1.11(2H, m), 1.15-1.38(4H, m), 1.63-1.89(5H, m), 2.34(3H, s), 3.71(2H, d, J=7Hz), 3.74(3H, s), 5.15(2H, s), 6.36(1H, d, J=8Hz), 6.49(1H, d, J=16Hz), 6.70(1H, dd, J=2, 8Hz), 6.98(1H, d, J=2Hz), 7.34(1H, d, J=16Hz).

Mass(ESI) : m/z 437(M+1).

Preparation Example 23-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)-benzyl)-2-methylimidazol-5-yl)-2-propenic acid was obtained as thin

yellow crystals (375 mg) from methyl (E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenate (418 mg).

^{1}H-NMR($CDCl_3$) : 0.95-1.10(2H, m), 1.15-1 .38(4H, m), 1.64-1.89(5H, m), 2.35(3H, s), 3.71(2H, d, J=7Hz), 5.16(2H, s), 6.33(1H, d, J=8Hz), 6.46(1H, d, J=16Hz), 6.70(1H, dd, J=2, 8Hz), 7.00(1H, d, J=2Hz), 7.40(1H, d, J=16Hz).

Mass(ESI) : m/z 421(M-1).

Preparation Example 24-1

In the same manner as in the aforementioned Preparation Example 15-1, 1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazole-5-carboxyaldehyde was obtained as a yellow oil (410 mg) from 5-chloro-2-methylimidazole-4-carboxyaldehyde (200 mg) and 4-benzyloxy-2-chlorobenzyl chloride (480 mg).

^{1}H-NMR($CDCl_3$) : 2.32(3H, s), 5.02(2H, s), 5.57(2H, s), 6.47(1H, d, J=8Hz), 6.78(1H, dd, J=2, 8Hz), 7.05(1H, d, J=2Hz), 7.30-7.45(5H, m), 9.76(1H, s).

Mass(ESI) : m/z 375(M+1).

Preparation Example 24-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenate was obtained as a colorless oil (384 mg) from 1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazole-5-carboxyaldehyde (389 mg).

^{1}H-NMR($CDCl_3$) : 2.33(3H, s), 3.75(3H, s), 5.03(2H, s), 5.15(2H, s), 6.38(1H, d, J=8Hz), 6.50(1H, d, J=16Hz), 6.79(1H, dd, J=2, 8Hz), 7.08(1H, d, J=2Hz), 7.33(1H, d, J=16Hz), 7.31-7.43(5H, m).

Mass(ESI) : m/z 431(M+1).

Preparation Example 24-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenic acid was obtained as yellow crystals (296 mg) from methyl (E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenate (375 mg).

^{1}H-NMR($CDCl_3$) : 2.35(3H, s), 5.03(2H, s), 5.16(2H, s), 6.40(1H, d, J=8Hz), 6.47(1H, d, J=16Hz), 6.80(1H, dd, J=2, 8Hz), 7.0 9(1H, d, J=2Hz), 7.30-7.45(6H, m).

Mass(ESI) : m/z 415(M-1).

Preparation Example 25-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazole-5-carboxyaldehyde was obtained as a colorless oil (344 mg) from 5-chloro-2-methylimidazole-4-carboxyaldehyde (200 mg) and 2-chloro-1-((methanesulfonyloxy)methyl)-4-(methylthio)benzene (379 mg).

^{1}H-NMR($CDCl_3$) : 2.32(3H, s), 2.46(3H, s), 5.58(2H, s), 6.43(1H, d, J=8Hz), 7.03(1H, dd, J=2, 8Hz), 7.26(1H, overlapped with $CDCl_3$), 9.76(1H, s).

Mass(ESI) : m/z 315(M+1).

Preparation Example 25-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-2-propenate was obtained as a yellow oil (384 mg) from 4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazole-5-carboxyaldehyde (336 mg).

^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 2.47(3H, s), 3.75(3H, s), 5.17(2H, s), 6.36(1H, d, J=8Hz), 6.49(1H, d, J=16Hz), 7.04(1H, dd, J=2, 8Hz), 7.30(1H, d, J=2Hz), 7.32(1H , d, J=16Hz).

Mass(ESI) : m/z 371(M+1).

Preparation Example 25-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-2-propenic acid was obtained as thin yellow crystals (305 mg) from methyl (E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-2-propenate (374 mg).

^{1}H-NMR($CDCl_3$) : 2.35 (3H, s), 2.47(3H, s), 5.18(2H, s), 6.38(1H, d, J=8Hz), 6.47(1H, d, J=16Hz), 7.05(1H, dd, J=2, 8Hz), 7.30(1H, d, J=2Hz), 7.37(1H, d, J=16Hz).

Mass(ESI) : m/z 357(M+1).

Preparation Example 26-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazole-5-carboxyaldehyde (189 mg) was obtained as a pale-yellow solid from 5-chloro-2-methylimidazole-4-carboxyaldehyde (100 mg) and 2-chloro-4-(trifluoromethyl)benzyl bromide (378 mg).

^{1}H-NMR($CDCl_3$) : 2.35(3H, s), 5.65(2H, s), 6.60(1H, d, J=8Hz), 7.45(1H,

d, J=8Hz), 7.71(1H, s), 9.76(1H, s).
Mass(ESI) : m/e 337(M)+.

Pr paration Example 26-2

In the same manner as in the aforementioned Preparation Example 15-2, ethyl (E)-3-[4-chloro-1-(2-chloro-4-(trifluoromethyl)-benzyl)-2-methylimidazol-5-yl]-2-propenate (207 mg) was obtained as a colorless oil from 4-chloro-1-(2-chloro-4-(trifluoromethyl)-benzyl)-2-methylimidazole-5-carboxyaldehyde (185 mg).
^{1}H-NMR($CDCl_3$) : 1.30(3H, t, J=6Hz), 2.35(3H, s), 4.20(2H, q, J=6Hz), 5.36(2H, s), 6.54(1H, d , J=16Hz), 6.59(1H, d, J=8Hz), 7.26(1H, d, J=16Hz), 7.48(1H, d, J=8Hz), 7.75(1H, s).
Mass(ESI) : m/e 408(M+H)+.

Preparation Example 26-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid was obtained as colorless crystals (144 mg) from ethyl (E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-2-propenate (203 mg).
^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 5.26(2H, s), 6.49(1H, d, J=16Hz), 6.60(1H, d, J=8Hz), 7.33(1H, d, J=16Hz), 7.49(1H, d, J=8Hz), 7.75(1H, s).
Mass(ESI) : m/z 379(M+1).

Preparation Example 27-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-(2-chloro-4-(phenoxymethyl)benzyl)-2-methylimidazole-5-carboxyaldehyde (482 mg) was obtained as a colorless oil from 5-chloro-2-methylimidazole-4-carboxyaldehyde (216 mg) and 2-chloro-1-((methanesulfonyloxy)methyl)-4-(phenoxymethyl)benzene (605 mg).
^{1}H-NMR($CDCl_3$) : 2.33(3H, s), 5.01(2H, s), 5.63(2H, s), 6.51(1H, d, J=8Hz), 6.90-7.03(3H, m), 7.20-7.35(3H, m), 7.53(1H, d, J=2Hz), 9.77(1H, s).
Mass(ESI) : m/e 375(M+H)+.

Preparation Example 27-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)-benzyl)-2-methylimidazol-5-yl)-2-propenate (413 mg) was obtained as a white powder from 4-chloro-1-(2-chloro-4-(phenoxymethyl)-

benzyl)-2-methylimidazole-5-carboxyaldehyde (475 mg) and methyl (triphenylphosphoranylidene)acetate (623 mg).
^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 3.74(3H, s), 5.03(2H, s), 5.22(2H, s), 6.47(1H, d, J=8Hz), 6.50(1H, d, J=16Hz), 6.91-7.04(3H, m), 7.21-7.34(3H, m), 7.22(1H, d, J=16Hz), 7.57(1H, d, J=2Hz).
Mass(ESI) : m/e 431(M+H)+.

Preparation Example 27-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (391 mg) was obtained as a white powder from methyl (E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)-benzyl)-2-methylimidazol-5-yl)-2-propenate (404 mg).
^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 5.01(2H, s), 5.21(2H, s), 6. 46(1H, d, J=16Hz), 6.47(1H, d, J=9Hz), 6.89-7.02(3H, m), 7.20-7.34(3H, m), 7.34(1H, d, J=16Hz), 7.55(1H, d, J=2Hz).
Mass(ESI) : m/e 415(M-H)-.

Preparation Example 28-1

In the same manner as in the aforementioned Preparation Example 15-1, 4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazole-5-carboxyaldehyde (304 mg) was obtained as pale-yellow crystals from 4-chloro-2-methylimidazole-5-carboxyaldehyde (200 mg) and 2-chloro-1-((methanesulfonyloxy)methyl)-4-nitrobenzene (404 mg).
^{1}H-NMR($CDCl_3$) : 2.37(3H, s), 5.67(2H, s), 6.67(1H, d, J=8Hz), 8.06(1H, dd, J=8, 2Hz), 8.34(1H, d, J=2Hz), 9.75(1H, s).

Preparation Example 28-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-2-propenate (297 mg) was obtained as pale-yellow crystals from 4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazole-5-carboxyaldehyde (285 mg) and methyl (triphenylphosphoranylidene)acetate (546 mg).
^{1}H-NMR($CDCl_3$) : 2.35(3H, s), 3.74(3H, s), 5.29(2H, s), 6.52(1H, d, J=15Hz), 6.65(1H, d, J=8Hz), 7.27(1H, d, J=2Hz), 8 .08(1H, d, J=8, 2Hz), 8.36(1H, d, J=2Hz).

Preparation Example 28-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-2-propenic acid (233 mg) was obtained as

pale-orange crystals from methyl (E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-2-propenate (275 mg).
^{1}H-NMR(DMSO-d_6) : 2.32(3H , s), 5.56(2H, s), 6.28(1H, d, J=15Hz), 6.77(1H, d, J=8Hz), 7.22(1H, d, J=15Hz), 8.16(1H, dd, J=8, 2Hz), 8.41(1H, d, J=2Hz).

Preparation Example 29-1

In the same manner as in the aforementioned Preparation Example 15-1, (E)-4-chloro-1-(2-chloro-4-(2-phenylethenyl)benzyl)-2-methylimidazole-5-carboxyaldehyde was obtained as orange crystals (471 mg) from 5-chloro-2-methylimidazole-4-carboxyaldehyde (209 mg) and (E)-2-chloro-4-(2-phenylethenyl)benzyl bromide (489 mg).
^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 5.64(2H, s), 6.50(1H, d, J=8Hz), 6.99(1H, d, J=16Hz), 7.10(1H, d, J=16Hz), 7.25-7.42(4H, m), 7.50(2H, d, J=8Hz), 7.58(2H, s), 9.78(1H, s).
Mass(ESI) : m/z 371(M+1).

Preparation Example 29-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-2-propenate was obtained as yellow amorphous (433 mg) from (E)-4-chloro-1-(2-chloro-4-(2-phenylethenyl)benzyl)-2-methylimidazole-5-carboxyaldehyde (390 mg).
^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 3.74(3H, s), 5.22(2H, s), 6.45(1H, d, J=8Hz), 6.51(1H, d, J=16Hz), 6.99(1H, d, J=16Hz), 7.12(1H, d, J=16Hz), 7.26-7.41(5H, m), 7.50(2H, d, J=8Hz), 7.60(1H, s).
Mass(ESI) : m/z 427(M+1).

Preparation Example 29-3

In the same manner as in the aforementioned Preparation Example 15-4, (2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)-benzyl)-2-methylimidazol-5-yl)-2-propenic acid was obtained as colorless crystals (326 mg) from methyl (2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-2-propenate (418 mg).
^{1}H-NMR(DMSO-d_6) : 2.34(3H, s), 5.41(2H, s), 6.26(1H, d, J=16Hz), 6.53(1H, d, J=8Hz), 7.18-7.44(6H, m), 7.51(1H, d, J=8Hz), 7.60(2H, d , J=8Hz), 7.84(1H, s).

Preparation Example 30-1

In the same manner as in the aforementioned Preparation Example

15-1, 1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazole-5-carboxyaldehyde (379 mg) was obtained as pale-yellow crystals from 4-chloro-2-methylimidazole-5-carboxyaldehyde (200 mg) and 1-bromo-2-(bromomethyl)naphthalene (457 mg).

^{1}H-NMR($CDCl_3$) : 2.32(3H, s), 5.88(2H, s), 6.58(1H, d, J=8Hz), 7.56(1H, t, J=8Hz), 7.65(1H, t, J=8Hz), 7.73(1H, d, J=8Hz), 7.82(1H, d, J=8Hz), 8.35(1H, d, J=8Hz), 9.82(1H, s).

Preparation Example 30-2

In the same manner as in the aforementioned Preparation Example 15-2, methyl (E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-2-propenate (413 mg) was obtained as pale-yellow crystals from 1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazole 5-carboxyaldehyde (386 mg) and methyl (triphenylphosphoranylidene)acetate (603 mg).

^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 3.70(3H, s), 5.44(2H, s), 6.50(1H, d, J=8Hz), 6.53(1H, d, J=2Hz), 7.37(1H, d, J=15Hz), 7.57(1H, t, J=8Hz), 7.67(1H, t, J=8Hz), 7.75(1H, d, J=8Hz), 7.83(1H, d, J=8Hz), 8.35(1H, d, J=8Hz).

Preparation Example 30-3

In the same manner as in the aforementioned Preparation Example 15-4, (E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-2-propenic acid (389 mg) was obtained as colorless crystals from methyl (E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-2-propenate (393 mg).

^{1}H-NMR(DMSO-d_6) : 2.37(3H, s), 5.61(2H, s), 6.24(1H, d, J=15Hz), 6.58(1H, d, J=8Hz), 7.24(1H, d, J=15Hz), 7.65(1H, t, J=8Hz), 7.76(1H, t, J=8Hz), 7.97(2H, t, J=8Hz), 8.29(1H, d, J=8Hz).

Example 1

To a suspension of (E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (155 mg) in N,N-dimethylformamide (0.8 ml) was added 1,1'-carbonyldiimidazole (101 mg) at room temperature, and the mixture was stirred for 1 hr. Thereto were added (4-methylbenzene)sulfonamide (106 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (96 mg), and the mixture was stirred at 50°C for 5 hr. The reaction mixture was ice-cooled and 1N hydrochlic acid (1.7 ml) was added dropwise to neutralize the solution. Water (4 ml) was added and the precipitate was collected by filtration. This crude product was recrystallized from acetone - water to give

(E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide (152 mg) as a pale-yellow powder.

^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 2.40(3H, s), 5.17(2H, s), 6.38(1H, d, J=8Hz), 6.49(1H, dd, J=3 and 2Hz), 6.53(1H, d, J=16Hz), 6.68(1H, d, J=3Hz), 7.31(2H, d, J=8Hz), 7.35(1H, d, J=16Hz), 7.43(1H, dd, J=8 and 2Hz), 7.49(1H, d, J=2Hz), 7.74(1H, d, J=2Hz), 7.92(2H, d, J=8Hz).

Mass(ESI) : m/e 528(M-H)-.

m.p. 242-243℃.

Example 2

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide (159 mg) was obtained as a pale-yellow powder from (E)-3-(4-chloro-1-(2-chloro-4-(2-furyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (148 mg) and (E)-(2-phenylethene)sulfonamide (108 mg).

^{1}H-NMR(DMSO-d_6) : 2.31(3H, s), 5.39(2H, s), 6.55(1H, d, J=8Hz), 6.61(1H, dd, J=3 and 2Hz), 6.69(1H, d, J=16Hz), 7.06(1H, d, J=3Hz), 7.26(1H, d, J=16Hz), 7.35-7.50(4H, m), 7.56(1H, d, J=16Hz), 7.59(1H, dd, J=8 and 2Hz), 7.67-7.77(2H, m), 7.78(1H, d, J=2Hz), 7.86(1H, d, J=2Hz), 12.07(1H, br s).

Mass(ESI) : m/e 540(M-H)-.

m.p. 227-228℃.

Example 3

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide was obtained as colorless crystals (80 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (100 mg) and (4-methylbenzene)sulfonamide (65 mg).

^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 2.40(3H, s), 5.16(2H, s), 6.37(1H, d, J=8Hz), 6.54(1H, d, J=16Hz), 7.06-7.11(1H, m), 7.26-7.40(6H, m), 7.65(1H, d, J=2Hz), 7.92(2H, d, J=8Hz).

Mass(ESI) : m/z 544(M-1).

m.p. 235-237℃.

Example 4

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-

phenylethenyl)sulfonyl)-2-propenamide was obtained as colorless crystals (105 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(2-thienyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (100 mg) and (E)-(2-phenylethene)sulfonamide (70 mg).

^{1}H-NMR(DMSO-d_6) : 2.32(3H, s), 5.39(2H, s), 6.52(1H, d, J=8Hz), 6.69(1H, d, J =16Hz), 7.11-7.17(1H, m), 7.26(1H, d, J=16Hz), 7.36-7.49(4H, m), 7.50-7.63(4H, m), 7.72(2H, dd, J=2, 8Hz), 7.84(1H, d, J=2Hz).

Mass(ESI) : m/z 556(M-1).

m.p. 246-248℃.

Example 5

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide was obtained as thin yellow crystals (123 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (130 mg) and (4-methylbenzene)sulfonamide (81 mg).

^{1}H-NMR($CDCl_3$) : 2.32(3H, s), 2.41(3H, s), 5.17(2H, s), 6.34(1H, d, J=8Hz), 6.56(1H, d, J=16Hz), 7.27-7.40(7H , m), 7.48-7.55(2H, m), 7.60(1H, d, J=2Hz), 7.93(2H, d, J=8Hz).

Mass(ESI) : m/z 562(M-1).

m.p. 239-241℃.

Example 6

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide was obtained as thin ocher crystals (101 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(phenylethynyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (130 mg) and (E)-(2-phenylethene)sulfonamide (87 mg).

^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 5.20(2H, s), 6.39(1H, d, J=8Hz), 6.61(1H, d, J=16Hz), 7.05(1H, d, J=16Hz), 7.30(1H, dd, J=2, 8Hz), 7.33-7.44(7H, m), 7.46-7.55(4H, m), 7.60(1H, d, J=2Hz), 7.71(1H, d, J=16Hz).

Mass(ESI) : m/z 574(M-1).

m.p. 220-222℃.

Example 7

In the same manner as in Example 1, (E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide (162 mg) was obtained as colorless crystals from (E)-3-(1-(4-bromo-2-chlorobenzyl)-4-

chloro-2-methylimidazol-5-yl)-2-propenic acid (150 mg) and (4-methylbenzene)sulfonamide (99 mg).

^{1}H-NMR($CDCl_3$) : 2.31(3H, s), 2.43(3H, s), 5.10(2H, s), 6.23(1H, d, J=8Hz), 6.58(1H, d, J=15Hz), 7.25-7.33(4H, m), 7.58(1H, d, J=2Hz), 7.92(2H, d, J=8Hz).

Mass(ESI) : m/z 542(M-H)-.

m.p. 233-235℃.

Example 8

In the same manner as in Example 1, (2E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide (172 mg) was obtained as colorless crystals from (E)-3-(1-(4-bromo-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenic acid (168 mg) and (E)-(2-phenylethene)sulfonamide (118 mg).

^{1}H-NMR($CDCl_3$ - CD_3OD) : 2.32(3H, s), 5.15(2H, s), 6.28(1H, d, J=8Hz), 6.70(1H, d, J=15Hz), 7.08(1H, d, J=15Hz), 7.31-7.42(5H, m), 7.49-7.53(2H, m), 7.62(1H, d, J=2Hz), 7.69(1H, d, J=15Hz).

Mass(ESI) : m/z 554(M-H)-.

m.p. 250-251℃.

Example 9

In the same manner as in Example 1, (E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-N-(1-pentanesulfonyl)-2-propenamide (134 mg) was obtained as colorless crystals from (E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenic acid (150 mg).

^{1}H-NMR($CDCl_3$) : 0.87(3H, t, J=8Hz), 1.24-1.45(4H, m), 1.75-1.89(2H, m), 2.40(3H, s), 3.38-3.47(2H, m), 5.26(2H, s), 6.50 (1H, d, J=8Hz), 6.57(1H, d, J=15Hz), 7.35-7.58(7H, m), 7.68(1H, d, J=2Hz), 8.18(1H, br s).

Mass(ESI) : m/z 520(M+1).

m.p. 203-204℃.

Example 10

In the same manner as in Example 1, (E)-N-benzenesulfonyl-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenamide (141 mg) was obtained as colorless crystals from (E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenic acid (150 mg).

^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 5.20(2H, s), 6.43(1H, d, J=8Hz), 6.57(1H,

d, J=15Hz), 7.31-7.55(9H, m), 7.59(1H, d, J=8Hz), 7.64(1H, d, J=2Hz), 8.05(2H, d, J=8Hz), 8.54(1H, br s).

Mass(ESI) : m /z 526(M+1).

m.p. 245-247℃.

Example 11

In the same manner as in Example 1, (E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-N-((4-methylbenzene)sulfonyl)-2-propenamide (137 mg) was obtained as colorless crystals from (E)-3-[4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl]-2-propenic acid (150 mg).

^{1}H-NMR($CDCl_3$) : 2.35(3H, s), 2.40(3H, s), 5.19(2H, s), 6.43(1H, d, J=8Hz), 6.57(1H, d, J=15Hz), 7.24-7.55(8H, m), 7.65(1H, d, J=1Hz), 7.92(2H, d, J=8Hz), 8.41(1H, br s).

Mass(ESI) : m/z 540(M+1).

m.p. 229-232℃.

Example 12

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide (132 mg) was obtained as colorless crystals from (E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-2-propenic acid (150 mg) and (E)-(2-phenylethene)sulfonamide (106 mg).

^{1}H-NMR($CDCl_3$) : 2.37(3H, s), 5.22(2H, s), 6.47(1H, d, J=8Hz), 6.57(1H, d, J=15Hz), 7.03(1H, d, J=15Hz), 7.37-7.54(12H, m), 7.65(1H, s), 7.71(1H, d, J=15Hz).

Mass(ESI) : m/z 554(M+H)+.

m.p. 240-241℃.

Example 13

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-N-(5-chloro-2-thienyl)sulfonyl)-2-propenamide (126 mg) was obtained as colorless crystals from (E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-2-propenic acid (150 mg) and 5-chlorothiophene-2-sulfonamide (115 mg).

^{1}H-NMR($CDCl_3$) : 2.37(3H, s), 5.21(2H, s), 6.46(1H, d, J=8Hz), 6.60(1H, d, J=15Hz), 6.90(1H, d, J=4Hz), 7.37-7.53(7H, m), 7.64-7.66(2H, m).

Mass(ESI) : m/z 566(M+H)+.

m.p. 229-23 3℃.

Example 14

In the same manner as in Example 1, (E)-N-(5-bromo-2-thienyl)sulfonyl-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-2-propenamide (155 mg) was obtained as colorless crystals from (E)-3-(4-chloro-1-(2-chloro-4-phenylbenzyl)-2-methylimidazol-5-yl)-2-propenic acid (150 mg) and 5-bromothiophene-2-sulfonamide (141 mg).

^{1}H-NMR($CDCl_3$) : 2.37(3H, s), 5.21(2H, s), 6.46(1H, d, J=8Hz), 6.59(1H, d, J=15Hz), 7.04(1H, d, J=4Hz), 7.36-7.55(7H, m), 7.61(1H, d, J=4Hz), 7.66(1H, d, J=2Hz).

Mass(ESI) : m/z 612(M+H)+.

m.p. 234-235℃.

Example 15

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide (155 mg) was obtained as colorless crystals from (E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (145 mg) and (4-methylbenzene)sulfonamide (96 mg).

^{1}H-NMR($CDCl_3$ - CD_3OD) : 1.02(3H, t, J=7Hz), 1.73-1.85(2H, m), 2.30(3H, s), 2.41(3H, s), 3.88(2H, t, J=7Hz), 5.10(2H, s), 6.27(1H, d, J=8Hz), 6.64(1H, d, J=15Hz), 6.68(1H, dd, J=8, 2Hz), 6.97(1H, d, J=2Hz), 7.27-7.33(3H, m), 7.92(2H, d, J=8Hz).

Mass(ESI) : m/z 520(M-H)-.

m.p. 226-228℃.

Example 16

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide (164 mg) was obtained as colorless crystals from (E)-3-(4-chloro-1-(2-chloro-4-(1-propoxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (143 mg) and (E)-(2-phenylethene)sulfonamide (106 mg).

^{1}H-NMR($CDCl_3$ - CD_3OD) : 1.02(3H, t, J=7Hz), 1.73-1.85(2H, m), 2.32(3H, s), 3. 88(2H, t, J=7Hz), 5.15(2H, s), 6.33(1H, d, J=8Hz), 6.69(1H, d, J=15Hz), 6.70(1H, dd, J=8, 2Hz), 6.98(1H, d, J=2Hz), 7.09(1H, d, J=15Hz), 7.35-7.42(4H, m), 7.50-7.54(2H, m), 7.68(1H, d, J=15Hz).

Mass(ESI) : m/z 532(M-H)-.

m.p. 199-201℃.

Example 17

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide was obtained as colorless crystals (60 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (100 mg) and (4-methylbenzene)sulfonamide (65 mg).

^{1}H-NMR($CDCl_3$) : 0.93(3H, t, J=7Hz), 1.3 0-1.50(4H, m), 1.70-1.84(2H, m), 2.32(3H, s), 2.42(3H, s), 3.90(2H, t, J=7Hz), 5.09(2H, s), 6.27(1H, d, J=8Hz), 6.53(1H, d, J=16Hz), 6.67(1H, dd, J=2, 8Hz), 6.96(1H, d, J=2Hz), 7.28-7.39(3H, m), 7.93(2H, d, J=8Hz).

Mass(ESI) : m/z 548(M-1).

m.p. 195-197℃.

Example 18

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide was obtained as colorless crystals (84 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(1-pentoxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (100 mg) and (E)-(2-phenylethene)sulfonamide (69 mg).

^{1}H-NMR($CDCl_3$) : 0.92(3H, t, J=7Hz), 1.30-1.49(4H, m), 1.69-1.72(2H, m), 2.34(3H, s), 3.90(2H, t, J=7Hz), 5.13(2H, s), 6.32(1H, d, J=8Hz), 6.56(1H, d, J=16Hz), 6.68(1H, dd, J=2, 8Hz), 6.96(1H, d, J=2Hz), 7.06(1H, d, J=16Hz), 7.35-7.56(6H, m), 7.72(1H, d, J=16Hz).

Mas s(ESI) : m/z 560(M-1).

m.p. 196-199℃.

Example 19

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-N-(1-pentanesulfonyl)-2-propenamide (82 mg) was obtained as a white powder from (E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)-methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (164 mg) and 1-pentanesulfonamide (90 mg).

^{1}H-NMR($CDCl_3$) : 0.90(3H, t, J=7Hz), 1.25-1.92(14H, m), 2.34(1H, sept, J=7Hz), 2.37(3H, s), 3.38-3.50(2H, m), 3.80(2H, d, J=7Hz), 5.16(2H, s), 6.34(1H, d, J=8Hz), 6.51(1H, d, J=15Hz), 6.72(1H, dd, J=8 and 2Hz), 7.00(1H, d, J=2Hz), 7.44(1H, d, J=16Hz).

Mass(ESI) : m/e 54 0 (M-H)-.

m.p. 177-178°C.

Example 20

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide (135 mg) was obtained as a white powder from (E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)-methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (163 mg) and (4-methylbenzene)sulfonamide (106 mg).

^{1}H-NMR($CDCl_3$) : 1.25-1.92(8H, m), 2.32(3H, s), 2.33(1H, sept, J=7Hz), 2.42(3H, s), 3.78(2H, d, J=7Hz), 5.09(2H, s), 6.27(1H, d, J=8Hz), 6.52(1H, d, J=16Hz), 6.68(1H, dd, J=8 and 2Hz), 6.97(1H, d, J=2Hz), 7.32(2H, d, J=8Hz), 7.34(1H, d, J=16Hz), 7.94(2H, d, J =8Hz).

Mass(ESI) : m/e 560(M-H)-.

m.p. 217-218°C.

Example 21

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide (128 mg) was obtained as a white powder from (E)-3-(4-chloro-1-(2-chloro-4-((cyclopentyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (164 mg) and (E)-(2-phenylethene)sulfonamide (99 mg).

^{1}H-NMR($CDCl_3$) : 1.23-1.92(8H, m), 2.32(1H, sept, J=7Hz), 2.33(3H, s), 3.77(2H, d, J=7Hz), 5.12(2H, s), 6.32(1H, d, J=8Hz), 6.60(1H, d, J=16Hz), 6.68(1H, dd, J=8 and 2Hz), 6.96(1H, d, J=2Hz), 7.08(1H, d, J=16Hz), 7.33-7.56(5H, m), 7.40(1H, d, J=16Hz) , 7.70(1H, d, J=16Hz).

Mass(ESI) : m/e 572(M-H)-.

m.p. 200-201°C.

Example 22

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide was obtained as colorless crystals (61 mg) from (E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (85 mg) and (4-methylbenzene)sulfonamide (52 mg).

^{1}H-NMR($CDCl_3$) : 0.95-1.89(11H, m), 2.32(3H, s), 2.42(3H, s), 3.70(2H, d, J=7Hz), 5.10(2H, s), 6.22(1H, d, J=8Hz), 6.50(1H, d, J=16Hz), 6.67(1H, dd, J=2, 8Hz), 6.97(1H, d, J=2Hz), 7.30-7.38(3H, m), 7. 94(2H, d, J=8Hz).

Mass(ESI) : m/z 574(M-1).

m.p. 214-216℃.

Exampl 23

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide was obtained as colorless crystals (63 mg) from (E)-3-(4-chloro-1-(2-chloro-4-((cyclohexyl)methyloxy)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (85 mg) and (E)-(2-phenylethene)sulfonamide (55 mg).

^{1}H-NMR($CDCl_3$) : 0.95-1.37(6H, m), 1.65-1.88(5H, m), 2.35(3H, s), 3.70(2H, d, J=7Hz), 5.13(2H, s), 6.31(1H, d, J=8Hz), 6.54(1H, d, J=16Hz), 6.68(1H, dd, J=2, 8Hz), 6.98(1H, d, J=2Hz), 7.06(1H, d, J=16Hz), 7.37-7.45(4H, m), 7.49-7.54(2H, m), 7.72(1H, d, J=16Hz).

Mass(ESI) : m/z 586(M-1).

m.p. 210-212℃.

Example 24

In the same manner as in Example 1, (E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide was obtained as colorless crystals (83 mg) from (E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenic acid (90 mg) and (4-methylbenzene)sulfonamide (55 mg).

^{1}H-NMR($CDCl_3$) : 2.32(3H, s), 2.42(3H, s), 5.03(2H, s), 5.10(2H, s), 6.29(1H, d, J=8Hz), 6.51(1H, d, J=16Hz), 6.75(1H, dd, J=2, 8Hz), 7.06(1H, d, J=2Hz), 7.29-7.44(8H, m), 7.95(2 H, d, J=8Hz).

Mass(ESI) : m/z 568(M-1).

m.p. 226-228℃.

Example 25

In the same manner as in Example 1, (2E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide was obtained as colorless crystals (73 mg) from (E)-3-(1-(4-benzyloxy-2-chlorobenzyl)-4-chloro-2-methylimidazol-5-yl)-2-propenic acid (90 mg) and (E)-(2-phenylethene)sulfonamide (59 mg).

^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 5.02(2H, s), 5.14(2H, s), 6.34(1H, d, J=8Hz), 6.56(1H, d, J=16Hz), 6.77(1H, dd, J=2, 8Hz), 7.02-7.10(2H, m), 7.31-7.55(11H, m), 7.73(1H, d, J=16Hz).

Mass(ESI) : m/z 580(M-1).

m.p. 225-227℃.

Example 26

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide was obtained as colorless crystals (83 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (90 mg) and (4-methylbenzene)sulfonamide (65 mg).

^{1}H-NMR($CDCl_3$) : 2.32(3H, s), 2.42(3H, s), 2.47(3H, s), 5.11(2H, s), 6.26(1H, d, J=8Hz), 6.52(1H, d, J=16Hz), 7.00(1H, dd, J=2, 8Hz), 7.26-7.36(4H, m), 7.94(2H, d, J=8Hz).

Mass(ESI) : m/z 508(M-1).

m.p. 228-230℃.

Example 27

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide was obtained as colorless crystals (97 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(methylthio)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (90 mg) and (E)-(2-phenylethene)sulfonamide (69 mg).

^{1}H-NMR($CDCl_3$) : 2.34(3H, s), 2.46(3H, s), 5.15(2H, s), 6.31(1H, d, J=8Hz), 6.57(1H, d, J=16H z), 7.00(1H, d, J=2Hz), 7.05(1H, d, J=16Hz), 7.29(1H, d, J=2Hz), 7.35-7.45(4H, m), 7.49-7.55(2H, m), 7.72(1H, d, J=16Hz).

Mass(ESI) : m/z 520(M-1).

m.p. 237-238℃.

Example 28

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide was obtained as thin yellow crystals (14 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (30 mg) and (4-methylbenzene)sulfonamide (20 mg).

^{1}H-NMR($CDCl_3$) : 2.33(3H, s), 2.42(3H, s), 5.20(2H, s), 6.48(1H, d, J=8Hz), 6.60(1H, d, J=16Hz), 7.23-7.35(3H, m) , 7.44(1H, d, J=8Hz), 7.72(1H, s), 7.92(2H, d, J=8Hz).

Mass(ESI) : m/z 530(M-1).

m.p. 223-225℃.

Exampl 29

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide was obtained as colorless crystals (90 mg) from (E)-3-(4-chloro-1-(2-chloro-4-(trifluoromethyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (100 mg) and (E)-(2-phenylethene)sulfonamide (72 mg).

^{1}H-NMR(DMSO-d_6) : 2.30(3H, s), 5.48(2H, s), 6.63-6.75(2H, m), 7.24(1H, d, J=16Hz), 7.37-7.51(4H, m), 7.57(1H, d, J=16Hz), 7.66(1H, d, J=8Hz), 7.73(2H, d, J=8Hz), 7.99(1H, s).

Mass(ESI) : m/z 542(M-1).

m.p. 261-263℃.

Example 30

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide (207 mg) was obtained as a white powder from (E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)-benzyl)-2-methylimidazol-5-yl)-2-propenic acid (191 mg) and (4-methylbenzene)sulfonamide (118 mg).

^{1}H-NMR($CDCl_3$) : 2.32(3H, s), 2.42(3H, s), 5.02(2H, s), 5.16(2H, s), 6.38(1H, d, J=8Hz), 6.54(1H, d, J=15Hz), 6.89-7.04(3H, m), 7.18-7.38(6H, m), 7.54(1H, d, J=2Hz), 7.93(2H, d, J=8Hz).

Mass(ESI) : m/e 568(M-H)-.

m.p. 236-237℃.

Example 31

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide (219 mg) was obtained as a white powder from (E)-3-(4-chloro-1-(2-chloro-4-(phenoxymethyl)-benzyl)-2-methylimidazol-5-yl)-2-propenic acid (189 mg) and (E)-(2-phenylethene)sulfonamide (128 mg).

^{1}H-NMR($CDCl_3$) : 2.30(3H, s), 5.07(2H, s), 5.39(2H, s), 6.50(1H, d, J=8Hz), 6.70(1H, d, J=16Hz), 6.88-7.02(3H, m), 7.22(1H, d, J=16Hz), 7.26-7.48(7H, m), 7.56(1H, d, J=16Hz), 7.62(1H, d, J=2Hz), 7.68-7.80(2H, m), 12.08(1H, br s).

Mass(ESI) : m/e 580(M-H)-.

m.p. 202-20 3℃.

Example 32

In the same manner as in Example 1, (E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide (63 mg) was obtained as pale-yellow crystals from (E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-2-propenic acid (105 mg) and (4-methylbenzene)sulfonamide (76 mg).

^{1}H-NMR($CDCl_3$ - CD_3OD) : 2.32(3 H, s), 2.41(3H, s), 5.24(2H, s), 6.55(1H, d, J=8Hz), 6.68(1H, d, J=15Hz), 7.22(1H, d, J=15Hz), 7.30(2H, d, J=8Hz), 7.90(2H, d, J=8Hz), 8.03(1H, dd, J=8, 2Hz), 8.33(1H, d, J=2Hz).

Mass(ESI) : m/z 507(M-H)-.

m.p. 241-243℃.

Example 33

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide (78 mg) was obtained as pale-yellow crystals from (E)-3-(4-chloro-1-(2-chloro-4-nitrobenzyl)-2-methylimidazol-5-yl)-2-propenic acid (105 mg) and (E)-(2-phenylethene)sulfonamide (81 mg).

^{1}H-NMR($CDCl_3$ - CD_3OD) : 2.34(3H, s), 5.29(2H, s), 6.59(1H, d, J=8Hz), 6.73(1H, d, J=15Hz), 7.06(1H, d, J=15Hz), 7.30(1H, t, J=8Hz), 7.37-7.45(3H, m), 7.50-7.52(2H, m), 7.68(1H, d, J=15Hz), 8.05(1H, dd, J=8, 2Hz), 8.34(1H, d, J=2Hz).

Mass(ESI) : m/z 519(M-H)-.

m.p. 199-201℃.

Example 34

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide was obtained as thin yellow crystals (81 mg) from (2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (150 mg) and (4-methylbenzene)sulfonamide (93 mg).

^{1}H-NMR($CDCl_3$) : 2.33(3H, s), 2.39(3H, s), 5.15(2 H, s), 6.35(1H, d, J=8Hz), 6.54(1H, d, J=16Hz), 6.97(1H, d, J=16Hz), 7.08(1H, d, J=16Hz), 7.21-7.41(7H, m), 7.50(2H, d, J=8Hz), 7.55(1H, d, J=2Hz), 7.92(1H, d, J=8Hz).

Mass(ESI) : m/z 564(M-1).

m.p. 237-239℃.

Example 35

In the same manner as in Example 1, (2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide was obtained as colorless crystals (86 mg) from (2E)-3-(4-chloro-1-(2-chloro-4-((E)-2-phenylethenyl)benzyl)-2-methylimidazol-5-yl)-2-propenic acid (150 mg) and (E)-(2-phenylethene)sulfonamide (100 mg).

^{1}H-NMR($CDCl_3$) : 2.36(3H, s), 5.20(2H, s), 6.40 (1H, d, J=8Hz), 6.58(1H, d, J=16Hz), 6.96(1H, d, J=16Hz), 7.04(1H, d, J=16Hz), 7.08(1H, d, J=16Hz), 7.26-7.54(12H, m), 7.58(1H, d, J=2Hz), 7.70(1H, d, J=16Hz).

Mass(ESI) : m/z 576(M-1).

m.p. 230-232℃.

Example 36

In the same manner as in Example 1, (E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-N-((4-methylbenzene)sulfonyl)-2-propenamide (182 mg) was obtained as colorless crystals from (E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-2-propenic acid (175 mg) and (4-methylbenzene)sulfonamide (111 mg).

^{1}H-NMR($CDCl_3$) : 2.30(3H, s), 2.38(3H, s), 5.33(2H, s), 6.42(1H, d, J=8Hz), 6.52(1H, d, J=15Hz), 7.23-7.26(2H, m), 7.37(1H, d, J=15Hz), 7.57(1H, t, J=8Hz), 7.65(1H, d, J=8Hz), 7.70(1H, d, J=8Hz), 7.80(1H, d, J=8Hz), 7.88(2H, d, J=8Hz), 8.31(1H, d, J=8Hz), 8.69(1H, br s).

Mass(ESI) : m/z 558(M-H)-.

m.p. 260-262℃.

Example 37

In the same manner as in Example 1, (2E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-N-(((E)-2-phenylethenyl)sulfonyl)-2-propenamide (188 mg) was obtained as colorless crystals from (E)-3-(1-(1-bromo-2-naphthyl)-4-chloro-2-methylimidazol-5-yl)-2-propenic acid (175 mg) and (E)-(2-phenylethene)sulfonamide (119 mg).

^{1}H-NMR(DMSO-d_6) : 2.33(3H, s), 5.59(2H, s), 6.56(1H, d, J=8Hz), 6 .70(1H, d, J=15Hz), 7.27(1H, d, J=15Hz), 7.37-7.48(4H, m), 7.53(1H, d, J=15Hz), 7.64(1H, t, J=8Hz), 7.69-7.75(3H, m), 7.94(2H, t, J=8Hz), 8.26(1H, d, J=8Hz).

Mass(ESI) : m/z 570(M-H)-.

m.p. 264-265℃.

【Effect of the Invention】

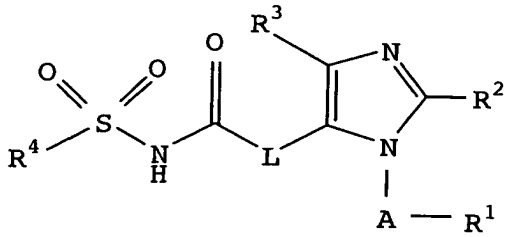
The above-mentioned imidazole compounds and pharmaceutically acceptable salts thereof of the present invention are useful as pharmaceutical preparations used for the prophylaxis and treatment of impaired glucose tolerance disorder, diabetes (e.g., type II diabetes), diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic bone resorption, diabetic glomerulosclerosis, diabetic nephropathy, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy and the like), insulin resistant syndrome (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberlig-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly and the like), polycystic ovary syndrome, hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure and the like), hyperglycemia (e.g., those characterized by abnormal saccharometabolism such as feeding disorders) and hypertension; and based on the cGMP-PDE (particularly PDE-V) inhibitory action, smooth muscle relaxing action, bronchodilating action, vasodilating action, smooth muscle cell inhibitory action, allergy inhibitory action and the like, they can be used for angina pectoris, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis), tubulointerstitial disorders (e.g., kidney diseases induced by FK506, cyclosporine and the like), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma inclusive of chronic asthma and allergic asthma), autoimmune diseases, allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility (e.g., hypersensitive enteropathy), impotence (e.g., organic impotence, psychic impotence and the like), nephritis, cancer cachexia or restenosis after PTCA, pancreatitis, cachexia (e.g., progressive weight loss due to lipolysis, myolysis, anemia, edema, anorexia and the like in chronic diseases such as cancer, tuberculosis, endocrine diseases and AIDS, and the like.

【Document】 Abstract

【Summary】

【Problems】 Provision of a compound useful for the prophylaxis and treatment of the diseases curable based on a hypoglycemic action, and the diseases curable based on a cGMP-PDE inhibitory action, a smooth muscle relaxing action, a bronchodilating action, a vasodilating action, a smooth muscle cell inhibitory action and an allergy inhibitory action.

【Solving Means】 An imidazole compound of the formula (I):



(I)

wherein each symbol is as defined in the specification, a salt thereof, and a pharmaceutical composition containing same.

【Main Drawing】 None